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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1948

THE PSYCHOSOMATIC APPROACH IN MEDICAL PRACTICE*

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THE proportionate consideration of physical and psychic factors in disease has been the medical ideal since the beginning of medicine as a discipline. In ancient Greece, Socrates, returning from army service, complained that the physicians of Hellas were less skillful than the barbarian Thracians. The latter realized that the body could not be cured without the mind, a reason that treatment of many diseases was unknown to the Greeks because they were "ignorant of the whole." Hippocrates, the Father of Medicine, also emphasized the need "to have knowledge of the whole of things" in order to bring about cure of the human body.[1] Without tracing the decline in such an idea which occurred in medicine in the intervening period we find the beginnings of our modern attempts to grasp "the whole of things" in medicine about 100 years ago. This is reviewed by Zilboorg[2] in a paper on the historical origins of psychosomatic medicine. He reminds us that, as late as the 18th century, psychiatry was chiefly the domain of the

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philosopher. Still in the early 19th century, preoccupation with the mental aspects of medicine was considered unscientific, a remnant of which attitude unfortunately still remains today. The accepted medical approach to mental ills was strictly in terms of the crude neuro-anatomy and pharmacology of the day. The physician interested in mental medicine, therefore, had the choice between a metaphysical approach and the crude organic one. Zilboorg also points out that the concept of the personality was slow to develop and that emotions, known as "passions," had a derogatory connotation. During this period the approach was chiefly ethical.

In 1840, however, a new attitude was crystallizing. The term "nervous disease" was introduced and was used interchangeably with "psychic" and "mental" disease, with the idea that every mental disease has a physical basis. This concept later reached a high point in 1869 with George Beard's theory of neurasthenia. In 1840, an Austrian physician used the phrase "psycho-physical totality of man." The term "personality disease" or "disturbance" was also coming into vogue. Even the term "psychosomatic," around which our discussion centers today, was anticipated in the title of a paper, "Further Discussions on the Somato-psychic Medicine," which appeared in the first volume of a new medical journal in 1838. This historical background is important to have in mind in realizing that our present emphasis on the organism as a whole is not an invention of the last 15 years but part of a recurring perspective in medicine which each time emerges with increased scientific knowledge and potency.

Our contemporary psychosomatic medicine, with its greatly added scientific armamentarium, is formed by a multitude of contributions in the last fifty years from clinical and laboratory medicine. Of special importance have been brilliant advances in endocrinology through the development of biological medicine, the physiological studies of Pavlov and Cannon, and the application of the discoveries and developments in psychoanalysis to the field of general medicine. Psychoanalysis is responsible for the establishment of the science of psychodynamics and has afforded a method of continuous and empirical study of the psyche and its bodily interrelationships, comparable in its own way to physiology and physiopathology of contemporary medicine.

There is some confusion as to the field that psychosomatic medicine embraces. In the narrower sense, it has been applied to the various

medical and surgical entities in which recent investigation has shown a large and, at times, predominantly emotional component. The better known of these are peptic ulcer, bronchial asthma, essential hypertension, Raynaud's disease, diabetes, spastic and ulcerative colitis, and a variety of dermatological conditions. The actual etiological role that personality disturbances and emotional conflict may play in these conditions awaits the further elucidation of the physiological as well as the psychological mechanisms operating. In a number of these, there is good reason to accept an important hereditary factor. This does not, however, exclude the importance of a functional trigger mechanism. Such terms as "essential hypertension" and "idiopathic ulcerative colitis" illustrate medical ignorance of the nature of the disease. Certainly any elucidation that psychological medicine can throw on the problem should be welcomed.

In the broader and, I believe, very acceptable sense, psychosomatic medicine applies to the approach enunciated at the beginning of this paper, indicating the physician's utilization, according to his training and experience, of both physical and psychological techniques in his treatment of patients. Strictly speaking, any reaction that has both psychic and physical components is psychosomatic; such are blushing, weeping, and physical expressions accompanying pleasure, anger, and anxiety. Wolf and Wolff[3] have shown, through study of a subject with a permanent gastric fistula, that flushing with anger or the pallor of fear appearing in the face may be duplicated in the mucous membrane of the stomach. Many purely psychiatric conditions, such as conversion hysteria, have accompanying physical manifestations and are in this sense psychosomatic. As mentioned, so-called organic physical disease may contain a large psychological factor. In addition to what might be considered causative, every physician is acquainted with secondary emotional reactions to physical disease, whatever its origin. In this discussion, I would like to stress the broader psychosomatic approach as it applies to the practitioner or the specialist. All such persons actually practice psychosomatic medicine whether they realize it or not.

It has always been accepted that some physicians are eminently successful because of their human understanding and can utilize this understanding to promote recovery of their patients. We also recognize the fact that the general practitioner in the small community, who

knows the background, family, and acquaintances of his patient, often intuitively or consciously utilizes this knowledge in helping him to make a diagnosis or outline treatment. The ability to utilize such knowledge and understanding of the patient's personality and background has been considered as a more or less intangible asset of the individual physician and put under the heading of the art of medicine. With the recent trend towards specialization, the tendency had been to put less emphasis on these so-called "intangibles" and concentrate instead on the physical aspects of the patient's problem through technical and laboratory procedures. Now, however, the practitioner is beginning to realize the necessity of also considering personality factors in making a correct diagnosis and in planning an intelligent treatment program. Psychiatry has been the field through which such an approach has been placed on a real scientific basis.

It is not sound, however, to expect the non-psychiatrist to become a specialist in the field of psychiatry. There never can, though, be enough psychiatrists adequately to care for the neuroses which require treatment. It is therefore not only logical but imperative that the practitioner, increasingly through his medical training, be initiated into the aid which psychiatric knowledge can give him in handling his case material.

With all the popularization of psychosomatic medicine, the practitioner is generally at a loss as to how to apply the principles. Some, fired by the appeal not to neglect the emotional factor, rush in and may do more harm than good. One of the first steps, of course, is to sense that there is difficulty in the emotional sphere. The question then comes whether the practitioner himself will do something about it or will refer the case for further opinion and treatment. It is no more excusable to ride rough-shod over the sensibilities of the patient out of determination to make him confess his conflicts than it is technically excusable for an untrained and inexperienced doctor to do abdominal surgery and manhandle delicate omental tissue. One of the things that many such patients fear most is that their disclosures will not be dealt with understandingly, but will be ridiculed, laughed at, or judged harshly. An even greater fear, particularly in the hospital, is that intimate disclosures will become common property of the medical and other associated personnel. The fact that society through the law protects the inviolability of certain information given to the physician as privileged communication is an indication of the care that should be

exercised in dealing with intimate personal information. Unfortunately, the patient's fear that such disclosures may become common knowledge is too frequently realized.

It makes all the difference in the world, both in gaining and in properly using such information, whether the investigator approaches the patient as a detective who may trick him out of a confession or as an understanding and sympathetic listener who will take his cues from the patient as to how far to go and how to use these confidences to the patient's advantage. We are beginning to make progress in the training of medical students in the proper procedure in examining personality and social factors. Unfortunately, as yet there are not sufficient courses and helpful literature for those who have been out of medical school for some time. A course offered this year through the auspices of the New York County Medical Society has been an important step in the right direction. It is my purpose in this communication to lay special stress on procedure and what represents sound practice in the psychosomatic field.

Dr. Adolph Meyer, dean of psychiatry in this country and one of the early advocates for consideration of the individual as a whole, taught for many years that psychotherapeutic treatment *begins with the taking of the psychiatric history*. This also holds for the taking of the medical history insofar as the patient is suffering from emotional disturbances. To go too fast in the investigation of emotional factors or not to go far enough are equally poor procedures. The questions which are asked or are not asked indicate to the patient the sensitivity of the examiner. There is another particularly important rule for the non-psychiatric practitioner to observe, and that is not to get too deeply into the emotional material to a point which he is not qualified to handle. Only experience can give one the clue in many cases, but this understanding is as necessary for the practitioner to acquire as to know where minor surgery ends and major surgery begins.

An important part of this essential experience is developed through facility in taking a psychosomatic history, which will give the physician many clues to diagnosis which he otherwise would miss. One of the cardinal points in the approach is to allow the patient to tell his own story and not be too intent on covering only the questions in the purely medical or surgical outline of examination. Over and over the psychiatrist sees patients who have been through the hands of many

practitioners and who often have been subjected to numerous operations, without ever having had the opportunity to tell what they knew about the origin of their own disorder.

A striking example of this type of case was a woman admitted to the New York State Psychiatric Institute some years ago, who over a period of some 15 years had had 13 operations. Eventual review of the psychiatric material raised the question as to whether her whole disorder was not really a neurosis and whether most, if not all, the operations would have been unnecessary. This patient in her youth had been engaged to a physician who did not marry her. She ended by marrying a tailor whom she felt to be far beneath her aspirations, and because she could never forget her disappointment, began going to doctors with the varied complaints that arose from her dissatisfaction, unconsciously seeking the sympathy and help of a substitute for her earlier fiancé. The surgeon often succumbs to the patient's conversion symptoms, especially when reinforced by demand for operation, little realizing that the patient's neurosis uses such operative procedure for unconsciously motivated gratification. With adequate dissemination of psychiatric indications and contraindications, such operations should be considered due to gross ignorance and an evidence of inadequate diagnostic study. Although this is an extreme case, such missed diagnoses are of all too common occurrence.

The practitioner will not have time, nor will it be necessary, to take a full psychosomatic history in any but special cases. Furthermore, it is often better not to take this all at one or two sittings, but to distribute it, as will be further discussed. Any psychosomatic history, however, to be at all complete, should include a personal history, with information on early neurotic habits in childhood; schooling, including the patient's reaction to classmates and teachers; and an occupational history, which often throws important light on crises precipitating psychosomatic disease when these refer to loss of a job, financial insecurity, or personal difficulties with a fellow-employee or the employer. There should also be information on the early family background (including parents and siblings), marital status, and, if the practitioner is able to elicit it unobtrusively and skillfully, some history of the sexual development and sexual status. This latter is the portion of the history which, either through its omission or through inept handling, accounts for many missed diagnoses and much inappropriate treatment.

It is often a complaint that the psychiatrist or analyst is only interested in the sexual history. The duty of a consultant as facetiously expressed in my medical student days was to do a rectal examination, the implication being that this was what was most often neglected and gave the key to many a missed diagnosis. The psychiatrist is placed in somewhat the same position as the hypothetical consultant. Frequently, this equally important biological aspect of the situation has not been investigated, though it may give the important clue to diagnosis and treatment.

I should like to give an example from a case already reported.[4] A 28-year-old married Italian woman with diabetes, who had been for six weeks on the metabolism ward, had been complaining for a month of persistent pains and paraesthesia under the breast and over the thighs, with pulling sensations reaching to the Achilles tendons in both legs. This discomfort was especially severe when she attempted to retire for the night and would often keep her walking the floor for hours. During the day, the skin sensitiveness over the affected area forced her to reduce contact of clothing to a minimum. She had become increasingly difficult to regulate; yet no physical basis for her pain had been discovered. The psychiatrist was called for an opinion. The patient had been known to have diabetes for three years. Further history obtained by the psychiatrist threw a strong suspicion that a long and severe difference with her family over her marriage may have been important in precipitating the diabetes. The condition, however, had been regulated by diet and insulin without much medical supervision until a month or so before admission when the husband had persuaded her to consult a medical specialist. About this time, her sugar began to increase and a month later was four plus, leading to her hospitalization. After her admission, she was sugar-free for two weeks and then developed the pains and spasms described, with spilling of sugar which continued despite increased insulin and careful regulation of diet.

The hospital records showed that glycosuria was severe when the pains were at their worst and became less or disappeared when she was comparatively free from pain and spasm.

The psychiatric picture was typical of conversion hysteria. Inquiry of the patient and her husband showed that, although they had been married for two years, she was still a virgin, sexual relations having been limited to interfemoral contact. The probable relation between her

symptoms and the sexual situation was discussed with the couple, and, following discharge from the hospital, the marriage was consummated. The patient was seen in all six times over a two-month period and then lost sight of. A check made a year and a half later brought the report that she had taken the psychiatrist's advice "to have a baby," which had been her interpretation of the suggestion of better sexual hygiene. She reported that she had one child nine months old and was well along with the second. Her diabetes had been stationary but gave her no trouble. Her pains in the legs had vanished "by themselves" about a month after she stopped coming to the clinic.

Studies made at the Presbyterian Hospital[5, 6] and elsewhere have established the fact that in many cases of diabetes it is fully as important to check on the emotional factors as on diet and exercise, and that the well-trained physician of the future will have this in mind. In many cases, the physician who becomes convinced that the patient must be cheating on the diet because of unexplained sugar will find the discrepancy in the personality area. This is particularly true in puberty and adolescence. We will not go into the question of the degree to which psychic conflict may precipitate diabetes. Experience shows, however, that frequently the time that regulation of the diabetes is undertaken is particularly opportune for some psychotherapy. The patient, from the first impact of the knowledge of his having such a serious disease, frequently reacts with a secondary depression. Some time spent in allowing him to discuss this situation with appropriate encouragement and education is indicated.

Another interesting development which is likely to occur at this initial point is that the administration of insulin, with the shocks which this frequently induces, often releases emotional discharges which may give important clues to current conflicts that may bear on later management of the disease.

One of the outstanding contributions which psychoanalysis has made to medicine is the scientific approach to an understanding of the patient-physician relationship. This was worked out originally for analytic patients because of the realization of the tremendous influence that the analyst has on the revival of early memories and the acting out of neurotic conflicts in the treatment. As a result, one of the important stages in the perfection of the psychoanalytic technique came from concentration on the understanding and management of the so-called

"transference situation."

The same principles that operate in an analysis, however, are also present to a greater or less extent in the relationship between any doctor and any patient. In fact, the same mechanism underlies, in varying degrees, the relationship between lawyer and client, teacher and pupil, pastor and parishioner, or any one of a number of professional or purely personal relationships.

Psychoanalysis has shown that the physician draws much of his intrinsic influence and authority from the fact that he reactivates in the patient attitudes which earlier obtained toward a parent, particularly the father, which tends also to reactivate the belief in magical thought which is part of the infant's and young child's orientation. The more neurotic the individual, the more exaggerated the magical power with which the physician may be invested. This phenomenon explains the success of cults and charlatanism even though the dogma propounded is without basis in adequate scientific training and experience. One of the things on which general medical practice has failed to capitalize, however, is the legitimate use of the reawakening of such archaic attitudes for the healing of body and mind.

Equipped with the experience of taking an adequate psychosomatic history, when this is indicated, and aware of the psychodynamic factors operating in the patient-physician relationship, the physician is in a position to make maximum use of his time and effort in clinical work; he is, in the sense that we have defined it, practicing psychosomatic medicine. How important it is for the therapist not to inject his own prejudices into the relationship has already been mentioned. It is necessary further to understand the reason for this in evaluating the influence which he exercises in the psychotherapeutic situation. Often the patient, after unburdening himself of some concern, may not only feel considerable mental relief, but there may be a corresponding amelioration of the psychically conditioned physical symptom. This is often multiplied over a series of contacts. The physician may be surprised because he is unaware of the dynamic situation which has been operating in treatment. If he realized, however, the role that he is playing for such a patient, he would know that often guilts that are not specifically expressed or hostilities that are not clearly enunciated are constantly being symptomatically manifested by the neurotically tense person. A sympathetic, understanding, and non-censorious attitude, which is after all

the essence of the scientific approach, can act to allay guilt about such things as early masturbation, infantile death wishes, masked guilty affection toward a parent.

It is not necessary for the physician to understand the psychodynamics operating. Many a humane and intuitive physician is constantly practicing such therapy, and his judgment in regard to human beings and their reactions in distress prevents him from the wrong sort of interference, which is in the nature of inappropriate activity and, instead of bringing relief, may aggravate the condition. That the physician should not act as a detective ferreting out hidden secrets has already been emphasized.

Particular care must be used in the attitude which the physician displays at a disclosure, not necessarily dramatic or sensational, which entails a moral issue. Earlier, in referring to the peculiar psychological position the physician holds in the unconscious mind of the patient, his authority was stressed. To whatever moral standards or experiences the physician may himself have become conditioned, he must remember that he is neither priest nor preacher and is not under obligation to strike home with some moral or religious truth which is in the domain of another profession. The patient, though the infringement confessed may be minimal or actually non-existent, is often loaded with unnecessary guilt which an unwarranted look or word may compound rather than decrease, with resultant accentuation of symptoms.

Furthermore, physicians aware of the emotional conflict may be unaware that direct advice regarding this may be useless or dangerous unless the patient himself is at the point at which he can profit by such advice, even if it does not deal with moral issues but comes rather from the physician's real grasp of the patient's needs. If not properly timed for the patient to act on it, such advice leads to further conflict. For example, the individual may be suffering from sexual frustration or need of a husband or child, but to point these out without the means of realization or the emotional stability to utilize opportunities at hand will lead to further discontent or ill-considered action, following which the last state of the patient may be worse than the first.

Even when the physician has considerable grasp of the psychodynamics operating and does not either take a moral attitude or give unwarranted advice, he still must check himself in giving injudicious interpretations of the patient's thoughts or behavior. The psychothera-

pist grasps the forces operating long before he is in a position to disclose these to the patient. Some of the greatest harm is done by amateur psychotherapists who, with some smattering of psychoanalytic knowledge, insist on interpreting a dream or symptomatic act directly to the patient. Not only may this lead to resentment on the part of the patient or throw him into a panic, but, if persisted in, may speed up the production of the deeper unconscious material, and the whole relationship may get badly out of hand. It is equally as important for the practitioner to realize that merely to listen continuously, thereby allowing the patient to get deeper and deeper into the material may be just as dangerous as unwarranted interpretation. In this matter of listening, it is necessary to know when to put on the brakes and what material the relatively inexperienced physician can handle with impunity. We all know that a person who is encouraged to tell a life story frequently falls in love with the listener. If the material tends to go too deeply and if the severity of the condition indicates it, the advice of the specialist, who is technically prepared to deal with such contingencies, should be sought. Unfortunately, there is no rule of the thumb that one can give; only a certain amount of experience can clarify the danger points.

The practitioner, general or specialist, can still work within the confines of his particular field and, through greater psychological insight, add to the effectiveness of his techniques, medical or surgical. In this connection, the effect of suggestion should be included in his psychodynamic understanding. The suggestibility of a patient can be an asset or liability according to how it is utilized.

First to dispose briefly of placeboes. I have no quarrel with those physicians who use them skillfully. Unfortunately, they are often used with the purpose of working on the credulity of the patient with the idea afterwards of exposing him in order to drive home the functional nature of a complaint. If used purely as suggestion, the deception should be kept a secret by the physician, at least until the patient has fully recovered. In general, placeboes that are pure fakes do little real good and tend to weaken good psychotherapy and undermine its right to a place in scientific medicine.

It is quite another matter, however, to obtain the maximum good from a drug or procedure by emphasizing its healing qualities. Recently an example came to my attention of the limiting of the usefulness of a medication by curtailing the patient's faith in it. An extremely tense

and jittery patient required the periodic administration of a sedative during the day. The patient had considerable faith in the effects of this drug and was able to get along with administration at fairly long intervals, until a physician explained that the effects of the medication could not possibly last more than four hours. Following this exposure of the suggestive factor in the drug, the patient would regularly have a return of his symptoms in full force at the end of the four-hour interval. Whether sedative, vitamin, or digitalis is prescribed, it is unnecessary to go into the limitations of the medication. Rather, the faith reposed in it by the patient should be intelligently reinforced, not, of course, in an insincere or exaggerated way.

Just as it is unwise to give interpretations of psychological material before the patient is ready for it, it is also poor medical practice to frighten the patient by unduly forcing other truths on him, for example, through injudicious revelation of a bad prognosis. It is true that the physician may not feel he should carry the full responsibility, with the possibility of the patient's sudden death, and that he should inform a responsible relative. However, to tell some patients with heart disease that they may have a sudden attack and die may add an anxiety state on top of a serious organic one. Even with some cardiacs who ideally might do better with restricted activity, too much restriction may, by increasing tension and restlessness, defeat the aim.

Neither should the patient be burdened with serious differences of opinion of experts, unless this is unavoidable, or discussion of other equally or more serious cases which he may inadvertently or advertently hear. A particularly damaging situation for some patients is evoked by their hearing such disagreement of opinion between specialists on a serious operation. For example, I recall the case of a nine-year-old child who overheard the opinions of two specialists, one of whom said in her presence that she would die if she were operated on and the other of whom said she would die if she were not. A later adult neurosis showed this situation to have been pivotal in a nuclear anxiety. Frequently on medical or surgical rounds, the patient overhears portions of such contradictory opinion or fragments that he does not understand, and on this builds an anxiety that may seriously interfere with management, coöperation, and convalescence. Discussion of the autopsy, for example, on the last similar case naturally gives rise to a train of disturbing thoughts to the patient who overhears it.

Under other conditions it is important for the patient to have definite information of a serious character. If the patient really wishes and needs to know the truth, the physician must use his judgment in imparting it; and under some conditions, particularly before surgical operations, it is imperative that the patient have an understanding of what awaits him. Therefore, preparation for operation should include proper psychological preparedness. The surgeon may be surprised both by the coöperativeness of the patient and the smoothness of convalescence if this preparation is done skillfully. Many children have kept lasting emotional scars from having been deceived or suddenly overpowered and anesthetized preceding a simple tonsillectomy. Adults may take an entirely different attitude toward a major operation, particularly one in which the loss of an organ or the aftermath in the way of modified function may be involved, if some clear explanation of what is to be done and what the expected results are to be is reviewed. Careful explanations preceding hysterectomy, also explaining artificial menopausal changes, are well worth the time and effort expended. It is much easier for a patient to reconcile himself to a loss that will occur than to one that has occurred.

Not only should a patient have an explanation of what is to be done, but also there should be an evaluation of the anxiety component before some procedures are instituted, because often a particular drug or procedure may be contraindicated on a particular occasion because of the amount of anxiety associated with the symptom. One of my associates at Presbyterian Hospital has made some extremely interesting observations of the importance of such a psychosomatic approach to some cases of bronchial asthma. As has been mentioned, bronchial asthma is one of the more strictly psychosomatic conditions. There is no question of the important role that allergy plays in many, perhaps the majority, of cases. We also know that the same symptom complex may be produced on a predominantly hysterical basis with all degrees in between the essentially physical and the neurotic.

In a very severe case of bronchial asthma with an undoubted neurotic component, Viola Bernard made the following observations during the patient's hospitalization when the patient was undergoing both intensive medical and psychotherapeutic treatment. The patient had three types of attacks—attacks of anxiety independent of asthma, attacks of asthma with a strong anxiety component, and attacks of asthma with

little detectable anxiety. Observation showed that certain medical treatment usually considered indicated for asthmatic attacks failed to bring results or at times even aggravated the condition, depending on the amount and distribution of the anxiety. For example, certain prodromal bronchiospasm or tachypnea which had a definite component of anxiety would usually be made worse by administration of adrenalin, while aminophyllin or a simple sedative, or both, would be more efficacious. At times even psychotherapy in the form of reassurance over the telephone was as useful as the aminophyllin or sedative. With full-blown bronchial attacks, those associated with considerable detectable anxiety would not be improved or would be worsened by adrenalin, but improved by aminophyllin or sedative, whereas in those cases with little detectable anxiety, or where, to use the technical expression, the anxiety was "bound," and the patient would outwardly be very calm before the attack, adrenalin would bring relief. In addition to a more primary anxiety that may have been the cause, overt or concealed, of an attack, there was frequently a secondary anxiety engendered by the attack itself, from the feeling of suffocation and oppression. Adrenalin did not aggravate this type, but by relieving the attack itself reduced the anxiety. It was also found that under certain circumstances, the patient failed to respond to the helium tent. Study showed that the patient had a phobia for closed places and that the panic of being in a tent often vitiated the beneficial effects of such procedure.

One of the great drawbacks for any extensive psychotherapy for the non-psychiatrist is the amount of time which it often takes and the fact that spending such time may lead the inexperienced too deeply into the neurosis. There is a great difference, however, in the efficacy of treatment if its psychological implications are recognized and appropriate means are applied in divided doses. I have already indicated that psychotherapeutic treatment starts with the taking of a proper psychosomatic history; also that the practitioner must use caution in getting too quickly and therefore too deeply into the material. Both because of time limitation and the need at times of distributing the history to prevent depth, the practitioner should learn to utilize the opportunities that he has for long, continued observation and treatment to the best psychotherapeutic advantage. The treatment of essential hypertension, where the patient may have to be followed frequently over long periods of time, often brings such an opportunity.

As the term indicates, we do not yet understand the etiology of essential hypertension. Heredity appears to play a role, but this is not a sufficient explanation since it also does in a number of other conditions about which we understand the mechanism and are able to do much to alleviate. The work of Goldblatt has stimulated new approaches to the problem; another such is the investigation of the role of the adrenal cortex in hypertension now under study at the Presbyterian Hospital in New York.[7]

Essential hypertension is considered a psychosomatic disease because of the important role personality factors appear to play in it. Carl Binger[8] and collaborators have emphasized the piling up of personal tragedy in many cases which leads to a crescendo or forte and the outbreak of the disease. The individual appears frequently to be caught between his inability to roll with the punch and take life's onslaughts passively or to express his aggression and hostility and attempt to end them by a frontal attack. An insoluble life situation is often the result.

I am not advocating that the practitioner tilt at windmills in such cases. One of the most pernicious effects, however, of hypertension is the secondary anxiety and neurosis that frequently becomes engrafted on the original condition and tends to enhance it. The apprehension that frequent examination with the sphygmomanometer may engender, with endless comparison of one finding with another, may invite this. It would be much more humane and less damaging to the patient's condition to keep the blood pressure findings a matter of strict scientific record and, where possible, use other symptoms for evaluation. Whatever procedure is used, however, to measure the pressure level, the physician should try gradually to piece together the life situation. The patient should be encouraged to discuss business, family, and social worries, and thus alleviate rather than compound the anxiety. If the life situation is indeed desperate, a review by a psychiatrist familiar with these problems would be indicated. The degree to which essential hypertension may be prevented or cured by psychotherapy still awaits determination, but this should not delay the application of more superficial psychotherapy and, when possible, prevent the secondary neurosis and perhaps even stem the progress of the disease.

One of the conditions frequently seen by both practitioner and gastro-enterologist is spastic colitis. The psychiatrist sees numerous patients who have been to practitioner after practitioner, have been through

repeated gastro-intestinal series, and have been subjected to varied procedures without the physician recognizing that in the majority of such cases, he is dealing with a pure psychosomatic disease. The depression and weeping often accompanying the condition, which usually mounts with repeated examinations and unsuccessful treatments by different physicians through whose hands they pass, is usually not recognized as being the expression of the original difficulty giving rise to the physical symptoms with a secondary engrafted neurosis resulting from the futility of treatment and confusion as to what is really wrong. With a parallel personal history of work, love, or family relationships, the true nature of the condition can often be uncovered and such depression and weeping can be capitalized on for treatment, through emotional rather than physical discharge.

Naturally, such an inquiry should be made cautiously and without burdening the patient with too much insight. Recently a case came to my attention that had lasted over two years. Finally an internist grasped the situation, but could not restrain himself from passing his knowledge on directly to the patient. He told her that she was suffering from some deep unconscious conflict, that she was depressed, and that she should not read newspapers or depressing books. It was left at that, however, without pointing the way out, which, if the physician could not have done so himself, he should have called in a psychiatrist to attempt. The patient promptly became depressed, could no longer read the newspapers, particularly any accounts of accidents or suicides, and had mounting and intolerable anxiety. The depression was there—the physician had not caused it, but he had brought it to the surface precipitately. This did lead indirectly to her eventually seeking psychiatric aid, but affords an example of the wrong way to go about it.

In an earlier lecture of this series, psychosomatic aspects of colitis were referred to. The emotional component of mucous colitis has long been known. Since 1930, when Cecil Murray made a psychological investigation of ulcerative colitis, this has been added as a psychosomatic disease. At the Presbyterian Hospital and elsewhere, where ulcerative colitis has been treated psychosomatically, extremely encouraging results have come from attention to the emotional factors.[9, 10]

Ulcerative colitis is a condition often necessitating long periods of hospitalization or confinement to home. The practitioner thus must of necessity make repeated visits. If, in addition to various, not too satis-

factory medical treatments that are in vogue, he takes occasion to review the personality and family constellation, he may find one of the cardinal conditions frequently encountered operating:

1) That the attack of colitis started within a few days of some situation which from that time on became a gnawing concern. This is not usually a dramatic traumatic situation, but something that the individual, due to emotional immaturity or adverse circumstances, finds it difficult to adjust to. This frequently is related to life situations like engagements, marriage, or the birth of a child.

2) The first situation is frequently associated with difficulty in breaking away and emancipation from a dominating figure, generally the mother, toward whom there is a great deal of unrecognized hostility.

3) The necessity frequently of modification of the life situation so that the patient is not continually under the domination of the mother or mother-substitute who impedes recovery. One patient characterized it succinctly: "My mother had rather have me ill at home than away and well."

We do not have time to go into details of such situations which can be found in the literature. Gradually, however, if the physician takes the trouble to inquire, the situation will often become apparent. The patient must have confidence that the physician is an ally and will not in the end betray him to the well-meaning despot from whom he seeks escape. A little extra time at the bedside or in the consulting room, distributed over the long period of medical supervision such conditions require, often will add up in the end to the equivalent of long interviews in a briefer space of time. Naturally such conferences cannot be carried out with the family or others (such as patients on the ward) present.

Summary

In this paper, the attempt has been made to bring the present concept of psychosomatic medicine into historical perspective and to clarify contemporary definitions, indicating preference for the broader concept of the term as applied to all significant reactions having both a physical and emotional component. Given this base, it is clear that every physician practices psychosomatic medicine, the question only being the type of practice.

Some of the basic principles of applied psychodynamics are indi-

cated, as well as the importance of them in treatment. The place of advice, suggestion, emotional catharsis, and interpretation is discussed with these principles in mind, and with particular emphasis on what the practitioner is in a position to do psychotherapeutically.

Without attempting to make the non-psychiatrist a specialist in the field, it is imperative that the practitioner, increasingly through his medical training, be initiated into the aid which psychiatric knowledge can give him in handling his case material. This holds for the non-psychiatric specialist as well as for the general practitioner. In this way, the physician will develop a competency in the field comparable at least with the working knowledge he has of other specialties, and thus will keep abreast of the best medical practice of the day.

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ENERGY METABOLISM IN OBESE PATIENTS*

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THE statements of obese patients that they do not lose weight even though they eat scarcely anything might have been discounted. But when Von Noorden and other early students of this condition reported that some obese persons under their observation lost little or no weight while they were receiving low calory diets, it was but natural to infer that these patients were suffering from some metabolic aberration. There followed a long and arduous search for an abnormality in the energy exchange that would explain this peculiar conduct.

Basal Metabolism: It was soon reported that obese persons produce less heat per kilogram of body weight in the resting postabsorptive state than do normal controls. Had the comparison been made on the basis of height, it would have been found that the heat production of obese persons was greater than normal. But Rubner, Lusk and others had demonstrated that the basal heat production of all mammals is proportional to the area of the body surface and that no such relation exists when either weight or height alone is used as a basis of comparison.

Subsequently E. F. Du Bois[1] and his brother devised a method for calculating the area of the body surface that is suitable for clinical use and his technique has been universally accepted and employed. A few simple calculations show that with height stationary, doubling of body weight increases the area of the body surface about 40 per cent. Accordingly, in the case where basal heat production per square meter does not change as weight is gained, the heat production per kilogram will have decreased by about 40 per cent of its original value when body weight has doubled. If the obesity has developed in an adult, height will not have changed, but the basal heat production will have increased at nearly one-half the rate of the weight gain. Hence per unit of height the heat is abnormally great in obese persons. This shows the essential

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TABLE I

TOTAL BASAL HEAT PRODUCTION OF FIVE OBESE WOMEN COMPARED WITH IDEAL VALUES

	Weight lb.	*Surface Area, sq. M.*	*Calories/Sq. M./Hr.*	*Total Calories/Hr.*
Ideal	129	1.59	36.5	58
Observed	238	2.06	35.5	73

fallacy of referring calories to weight as was done by the early workers in this field.

Subsequent students have without exception compared the heat produced to the surface area when they wanted to deal with metabolic rates.

Boothby and Sandiford[2] using modern techniques measured the heat production in 94 obese patients and found that in 81 per cent of them the rates were within the normal band. In three instances, the rates fell between minus 16 and minus 20 per cent and one patient produced heat at a rate more than 16 per cent above normal.

Strouse, Wang, and Dye[3] compared the rates of normal persons with those who were underweight and overweight. They found no significant differences.

Among 180 cases of extreme obesity Grafe[4] found only three in which there was a definite decrease in basal rate.

Since occasional persons in whom no detectable disease exists are found to have basal rates as low as minus 15 to minus 25 per cent, it is evident that obesity is not caused by a lessened expenditure of energy in the basal state.

In fact, the total heat production of obese persons is greater than it is in corresponding normal persons, because the surface area is abnormally large in the former group. Instructive data are contained in Table I, taken from the paper by Strang and Evans[5] who compared the average values obtained from five obese women with a hypothetical normal control. It is seen that even though the heat production per square meter of body surface in the obese group is well within the normal range, nevertheless the total heat production per hour is markedly increased due to the augmented surface area.

Specific Dynamic Effect: If the heat production of a person who

has been without food for eighteen hours and who has been reclining quietly, is recorded and he is then fed, he will shortly produce more heat than he did in the fasting state. The failure to respond in this way, would result in gain of weight, provided the person continued to ingest precisely the same number of calories and provided there was no change in activity.

Several authors attempted to attribute obesity to lessened caloric response to food. However, both Dürr[6] and Lauter[7] emphasized the great variability in the specific dynamic response exhibited by normal persons and cast doubts upon the interpretations of earlier investigations.

Strang and McClugage,[8] fully aware of the many hazards surrounding the measurement of the specific dynamic response to food, conducted their studies so painstakingly that they inspire great confidence. They recorded the total increase in heat production for the eight hours following the ingestion of a test meal. The average increase over the basal value in eight obese subjects was 58 calories, whereas the response of five normal persons was 51 calories. Evidently obesity is not attributable to lessened dynamic response to food.

Luxuskonsumption: Grafe[9] conceived the idea that the heat production is influenced by the quantity of food eaten. It was postulated that the twenty-four hourly expenditure of energy increases as intake of food increases after full allowance has been made for the calories of the basal metabolism, the specific dynamic response and activity. The opposite effect would be caused by underfeeding. Obesity would result when this mechanism failed to respond to overeating. Unfortunately the experiments that Grafe performed to substantiate this hypothesis were poorly conceived and quite unconvincing. Our own studies[10] give no support to Grafe's conception.

Total Metabolism: It has been repeatedly observed that obese persons who are certainly receiving only minimal quantities of food may fail to lose weight. Such paradoxical conduct could arise from some obscure metabolic abnormality that permits unusual conservation in the expenditure of energy. In that case the total heat production would be definitely less than the predicted value. Whether a disturbance of this sort does exist can be decided by recording the twenty-four hourly heat production. This may be done by indirect calorimetry with the subject enclosed in a respiration chamber. But the data will not be entirely adequate to answer the question, because the subject is neces-

TABLE II

ENERGY METABOLISM IN OBESE PATIENTS

INSENSIBLE LOSS OF WEIGHT

		Grams
Initial body weight		70,000
Food + Water	2,800	
Urine + Feces	1,600	
Difference	1,200	
Final body weight		70,000
Insensible loss of weight	1,200	

REMOVAL OF HEAT BY EVAPORATION OF WATER

I. L. = Water Vapor (I. W.) + $CO_2 - O_2$
I. W. = I. L. − ($CO_2 - O_2$)
I. W. × 0.58 = Heat removed by evaporation

When I. W. = 0.93 I.L., then I.L. × 0.93 × 0.58 = Cal. lost in outgoing water vapor.

sarily quite inactive and the periods are limited to twenty-four or possibly forty-eight consecutive hours. Both of these limitations can be avoided by using the insensible loss of weight as a basis for the calculations. This method rests on the following considerations: Water is evaporated continuously from the skin and lungs. This is a means of removing heat since it requires 0.58 calories to convert one gram of water from the liquid to the gaseous state at usual body temperatures. This evaporation of water causes a continuous loss of weight which is slightly increased by the respiratory exchange of gases since the weight of the outgoing CO_2 exceeds that of the ingoing O_2. This relationship is expressed by the following equation: $I.L. = I.W. + CO_2 - O_2$ where I.L. is insensible loss of weight and I.W. is the weight of the evaporated water. The loss of weight that occurs when the individual takes nothing by mouth and excretes no urine or feces, is the insensible loss of weight. When it is desired to measure this loss of weight for twenty-four hourly periods, it is merely necessary to add the weight of the ingesta to the initial body weight and the weight of the excreta to the final body weight and to subtract the second sum from the first one. The difference is the insensible loss of weight. These relationships are shown in Table II.

Evaporation of water takes place even when the sweat glands are completely inactive. This is the condition when violent exercise is

avoided and when the air is cool enough to permit complete comfort. Under these circumstances the weight of the water vapor varies from about 700 to 1500 grams per twenty-four hours in adults, depending upon size and activity. This corresponds to the removal of 406 calories (700 × .58) to 870 calories (1500 × .58) by this route.

Earlier students[11] had shown that there is a quantitative relationship between the hourly insensible loss and the basal metabolism. In order to determine whether the heat removed by vaporization of water is proportional to heat production for twenty-four hourly intervals on the part of persons who are leading their usual lives, the following procedures were carried out.[12] A number of individuals were placed on diets which were considered to be close to maintenance and an accurate body weight was obtained each morning at the same time under the same conditions. If there was progressive gain or loss of weight, the calories of the diet were adjusted appropriately until constancy of weight was achieved. It could then be assumed that the subjects were in energy balance and that the total loss of heat was equal to the calories of the diet. Since the composition of the diet was known, it was possible to calculate the weights of the CO_2 produced and of the O_2 absorbed. Subtraction of the difference between these two weights from the twenty-four hourly insensible loss of weight, gave the weight of the water vapor. This value was then converted to its heat equivalent by multiplying by 0.58, which is the amount of heat in calories required to change one gram of water from the liquid to the gaseous phase. From these data, the per cent of the total heat, removed by evaporation of water, was calculated. Table III shows the data obtained from twelve individuals. It will be seen that the total variation in heat removed by evaporation of water was only from 23.8 per cent to 25.2 per cent, even though the heat production varied from 2,200 to 3,600 calories per 24 hours. These studies indicate that human beings exhibit a striking tendency to rid themselves of a fixed per cent of the heat produced in twenty-four hours by vaporization of water, provided only that they are comfortable in regard to environment. Therefore total heat production can be calculated from the weight of the water vaporized. But this latter value can not be obtained directly from persons who are moving about freely. However, a few calculations show that the water vapor makes up from 93 per cent to 98 per cent of the insensible loss of weight depending upon whether relatively much or little carbohy-

TABLE III

PERCENTAGE OF TOTAL HEAT LOST BY EVAPORATION OF WATER

Age yr.	*Heat lost by Evaporation of water, Percent*	*Comment*
56	23.8	Diabetic Patient
30	24.2	Diabetic Patient
28	24.2	Chemist
24	24.4	Chemist
25	24.1	Medical Student
23	24.7	Graduate Student
24	25.2	Graduate Student
24	24.2	Student
18	24.3	Patient in bed
15	24.8	Patient in bed
18	24.8	Patient in bed
47	24.7	Patient in bed

TABLE IV

ENERGY METABOLISM IN OBESE PATIENTS

Heat Production = Insensible Loss × 0.93 × 0.58 × 4.08
0.93 × 0.58 × 4.08 = 2.20

Example of Calculation of Heat Production for 24 Hours from Insensible Loss of Weight

	Gms.		*Gms.*
First Body Wt.	158,450	Second Body Wt.	158,700
Food and Drink	2,920	Urine	1,200
		Stool	250
	161,370		160,150

Insensible Loss — 161,370 — 160,150 = 1,220. 1,220 × 2.20 = 2,684 Calories

drate is being metabolized. Accordingly the insensible loss of weight, a value easily obtained, can be used conveniently as the basis for calculating the heat production.

The following equation is applicable when maintenance diets of the usual mixed variety are fed: Heat = I.L. × 0.93 × 0.58 . 4.08. Simplified: Heat = I.L. × 2.2. Where 0.93 is the per cent of the insensible loss of weight that consists of water vapor; 0.58 is the factor for converting weight of water evaporated to heat (calories); 4.08 is the factor for deriving total heat from heat lost by vaporization. An example of the calculation is seen in Table IV.

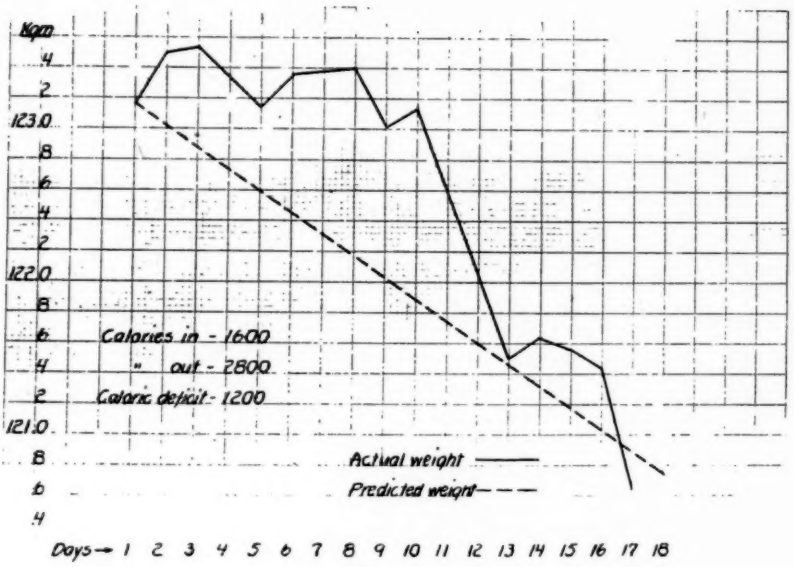

Fig. 1.

About 150 grams of body tissue were consumed daily to yield the 1200 calories not contained in the diet. Nevertheless, the body weight had declined only 100 grams by the tenth day. During the next three days, the patient lost about 1600 grams even though no change in diet had been made. The weight had now fallen to the value obtained by subtracting the weight of the body tissue destroyed during the thirteen days from the initial body weight.

In undernutrition, the same calculation is used except that the water vapor is now assumed to occupy 98 per cent of the insensible loss of weight since most of the heat is derived from the oxidation of fat. This difference is satisfied by multiplying I.L. by 2.3 instead of 2.2.

By means of this technique, the heat production of a number of obese persons was recorded consecutively in twenty-four hourly periods for several weeks and sometimes even for months. Included in the series were the various types of obesity described in the literature, namely: (1) a physically normal person except for the excessive weight, who frankly admitted years of gluttony, (2) a feeble-minded girl with a low basal rate, (3) a girl with disease of the pituitary body and a basal metabolic rate 30 per cent below normal, (4) a middle-aged woman whose weight had reached 295 pounds after an operation on the pitui-

TABLE V—ENERGY METABOLISM IN OBESE PATIENTS

FACTORS IN WATER BALANCE

Sources of Water	*Excretory Water*
1. Water of food	1. Water of urine
2. Water drunk	2. Water of stool
3. Water of oxidation	3 Insensible water
4. Preformed water	

tary body eight years earlier, (5) a young woman suffering from so-called Dercum's disease, (6) a middle aged woman five feet two inches tall, whose weight had reached 420 pounds–menopausal obesity. In no instance was the heat production less than the predicted value for comparable persons of normal weight. In fact, just the opposite was true. The obese patients invariably produced more heat per twenty-four hours than similar normal persons leading comparable lives.

Nevertheless, we, as had our predecessors, encountered obese patients who while receiving low calory diets, lost no weight for a number of days. An example of this phenomenon is found in Figure 1. The patient, a young woman, weighed 275 when she entered the hospital. Her basal metabolic rate per square meter of body surface was normal; but the total basal heat production was 2100 calories per twenty-four hours, about 600 calories greater than the predicted value for a comparable woman of normal weight. She remained in bed throughout the study. However, in spite of the inactivity, her twenty-four hourly heat production averaged 2800 calories. This was at least 800 calories greater than normal. Her diet contained 1600 calories daily. This produced a deficit of 1200 calories per day and calculation from the metabolic data indicated that she was oxidizing about 150 grams of body tissue daily as a source of these 1200 calories. Nevertheless, she lost only 100 grams during the first ten days. For the next three days, without any change in treatment, she lost about 1600 grams, and this was sufficient to bring her weight down to the predicted amount for that day. This very rapid loss of weight was far in excess of what could be explained by destruction of body tissue and compensated entirely for the stationary weight during the first ten days. Such a biphasic response suggested that the patient's body water was increasing progressively during the first phase in amounts whose weight roughly equalled that of the body

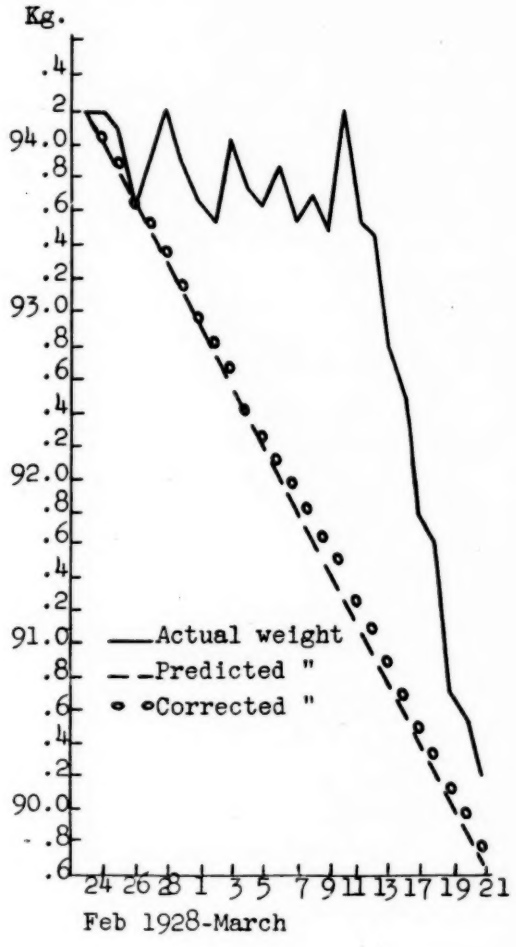

Fig. 2.

In spite of a daily deficit of 1225 calories, the patient weighed as much on the sixteenth day as she did on the first day. This was brought about by a progressive increase in body water. Subtraction of the weight of the excessive water from the actual body weight each day, gave values that agreed with the values obtained, by subtraction of the weights of the tissue destroyed from the actual body weights.

TABLE VI—ENERGY METABOLISM IN OBESE PATIENTS

RETENTION OF WATER CONCEALS DESTRUCTION OF TISSUE

Date 1929	*Change in Weight of Subject* *Grams*	*Weight of Body Tissue Destroyed* *Grams*	*Water Balance*
Feb. 3	+285	90	+369
Feb. 4	—225	90	—105
Feb. 5	+65	90	+149
Feb. 6	—125	90	—41
Feb. 7	+115	90	+198
Totals	+115	450	+570

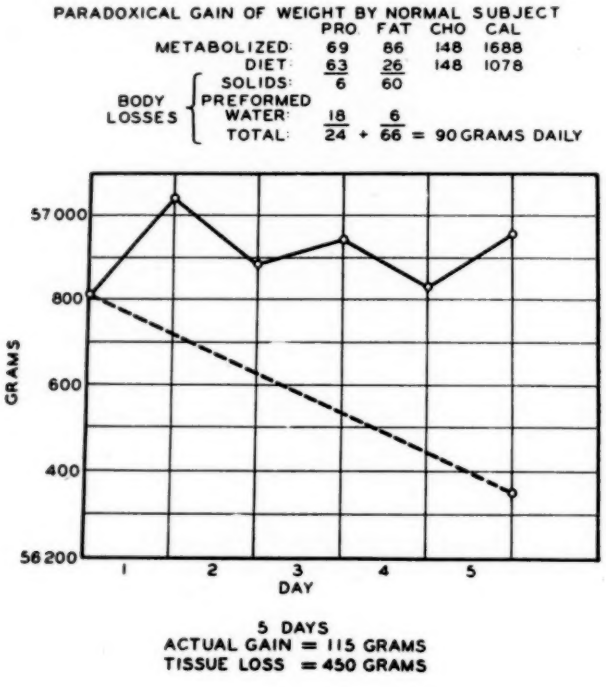

Fig. 3.

A normal man gains 115 grams in 5 days in spite of a daily deficit of 610 calories. The accompanying destruction of body tissue amounted to 450 grams. An addition of 565 (115 plus 450) grams of water to the body would permit the recorded gain in body weight. The calculations summarized in Table V indicate that 570 grams of excessive water had been retained by the body.

tissue being destroyed; and that in the second phase, the excessive water was excreted. Table V shows the various items that need to be taken into account in order to know whether water is being added to or lost from the organism. It should be noted that "preformed water" is that water which is an integral part of living tissue and which accordingly becomes an additional source of "free" water when tissue is destroyed. "Insensible water" is calculated from the insensible loss of weight as explained previously. The use of these methods in the study of obese patients showed that whenever weight was lost less rapidly, while they are being underfed, than predicted from the known weight of the destroyed tissue, the difference could be attributed to retention of water. Figure 2 is an example of this condition. The patient weighed the same on the sixteenth day as she did on the first one even though the daily caloric deficit amounted to 1225 calories. During the next nine days, the loss of weight was so rapid that for the whole twenty-four days, the total loss of weight closely approximated the expected loss calculated from the destruction of body tissue. The position of the circles in the diagram was obtained by subtracting the weight of the excessive body water from the actual weight. They show that the difference between the actual weight and what it would have been due to oxidation of body tissue if nothing else had intervened, is accounted for by water retention.

It is of further interest to realize that this accumulation of excessive water is not peculiar to obesity since the phenomenon occurs in normal persons who are receiving low calory diets. Figure 3 shows that a man of normal weight actually gained 115 grams in five days even though his diet contained 610 calories less than he produced per twenty-four hours. Table VI is the water exchange during this period. Since 450 grams of body tissue had been oxidized, it would have required the addition of 565 grams of water to the body to account for a gain of 115 grams of weight. The calculations gave an addition of 570 grams of water.

These periods of water retention may last for a few or many days and may recur frequently or occasionally. In any case they are always followed by periods of accelerated water loss that rid the organism of the excessive water. In time intervals of one or several months the patients will have lost the amount of weight corresponding to the destruction of body tissue.

Conclusions: The energy metabolism of obese patients is normal per square meter of body surface. The total twenty-four hourly heat production of obese persons is greater than normal in proportion to the increased surface area. Obesity is produced by prolonged inflow of energy that is greater than the outflow. To merely maintain an established body weight, obese persons must ingest more energy than comparable persons of normal weight.

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END RESULTS OF THORACOLUMBAR SYMPATHECTOMY FOR ADVANCED ESSENTIAL HYPERTENSION*†

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THE surgical treatment of hypertension had its origin in the pioneer work of Crile,[1] Adson and Craig,[2] Page and Heuer,[3] Peet[4] and others, but it was not until 1940 when Smithwick[5] first reported his clinical studies that an efficient operative procedure was made known. The method described by Smithwick and employed by him for the past nine years includes removal of the thoracolumbar chain from the 8th or 9th thoracic ganglion through the 1st or 2nd lumbar ganglion, along the portions of the greater, lesser, and least splanchnic nerves.

In a series of 375 thoracolumbar sympathectomies followed for six months to five years, we[6] have had 38 fatalities either in the hospital or within six months following operation. In an attempt to lower this mortality rate we analyzed the status of the 38 patients who died and that of the 337 surviving patients, and arrived at a set of rules which would reduce the mortality rate to 2.5 per cent. This figure is reasonably low in view of the fact that each patient undergoes two major operative procedures and many are recognized as poor risks.

Following the lead of Keith, Wagener and Barker[7] who graded the eyegrounds of hypertensive patients from 0 to 4 plus we have utilized a similar method for grading the cerebral, cardiac and renal status of each patient. In order to do this satisfactorily we require, in addition to a careful history and physical examination, the following studies: examination of the fundus, electrocardiography, a 6-foot heart plate, a concentration test (pitressin or Mosenthal), urea clearance, blood urea nitrogen, non-protein nitrogen and creatinine determinations and urinalysis. Intravenous urography was applied routinely in the work-

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TABLE I

RULES FOR EVALUATION OF SYMPTOMS IN INDICATIONS FOR OPERATION

Symbols Used	*Eyes*	*Cerebrum*	*Heart*	*Kidneys*
0	Normal	No Signs or Symptoms	No Signs or Symptoms	Normal
1 ±	Arteriolar Narrowing	Headaches and/or Dizziness and Nervousness	Slight Symptoms and/or Slight Enlargement and Slight E.K.G. Changes	Nocturia: But Concentration 1.024 or More: Urea Clearance 75% or More
2 +	Arteriolar Narrowing and Arterio-Venous Nicking	Headaches and/or Nosebleeds and/or Occipital Headaches and/or Dizziness and Nervousness	Moderate Symptom and/or Moderate X-ray Enlargement Moderate E.K.G. Changes	Urea Clearance 40-75% Concentration 1.015-1.023
3 +	Arteriolar Narrowing and Arterio-Venous Nicking and Hemorrhages and Exudates	Headaches and/or Nosebleeds and/or Occipital Headaches and/or Dizziness and Paresthesias	Marked Symptoms and/or Marked Enlargement and Marked E.K.G. Changes	Urea Clearance Less Than 40%; Concentration Less Than 1.015; Normal Blood Chemistry
4 +	Arteriolar Narrowing and Arterio-Venous Nicking and Hemorrhages and Exudates and Papilledema	Stroke or Encephalopathy or Confusion	Coronary Occlusion or Congestive Heart Failure	Persistent Elevation of N. P. N. to 40 Mgm. or More and B. U. N. to 20 Mgm. or More

up of the first 150 patients until one death and two marked reactions associated with the injection of dye caused us to abandon it unless there was a significant indication for its use.

In Table I we have outlined a system of rules which serve to evaluate the degree of damage present in each of the four important organs, brain, eye, kidney, and heart, as a result of the hypertensive state. Any

patient with ten or more pluses in all probability should not be operated upon.

A system such as this one, not based on mathematical data, must be interpreted in the light of clinical judgment, and it is implied that the operator has had a moderate amount of experience in the technique of thoracolumbar sympathectomy. The rules have aided us considerably and may be of help to internists and surgeons interested in the surgical treatment of hypertension.

It is very important to the surgeon and the internist to have clear-cut indications for accepting or rejecting these advanced cases for operation. It is our feeling that death occurring six months post-operatively indicates an unwise selection of patients for thoracolumbar sympathectomy. The only exception to this rule is the case in which papilledema has produced total blindness, and operation is performed to restore vision. Even when this objective is attained, it must be understood by the patient and his family that life expectancy will not be changed by this procedure.

Indications for Operation

Ocular Fundus: It may be stated categorically that in our experience no changes in the eyegrounds per se, with the exception of marked arteriosclerosis in conjunction with evidence of marked arteriosclerosis elsewhere, are to be thought of as contraindicating operation. Failing vision is in most cases an urgent criterion for operation, often in the face of other findings which ordinarily might be considered as militating against surgical intervention.

Cerebral Vessels: The status of the cerebral vessels has been the cause of great concern. Clinically attempts to predict occlusion or hemorrhage in the vessels of the brain are notoriously futile. However, in our experience aside from a persistent hemiplegia of less than six months duration, the most dependable evidence of cerebral damage, and therefore a contraindication to operation, is mental confusion, however slight, as evidenced by the usual signs of organic brain defects, particularly recent loss of memory. Such defects were most frequently seen in the presence of other signs of generalized arteriosclerosis. Parathesis, fainting attacks, dizzy spells and pounding headaches are discussed under medical indications.

Cardiac Status: In considering the cardiac status of a candidate for

sympathectomy, the most important consideration (granting a high degree of surgical competence and skillfully conducted anesthesia) is the history of functional cardiac capacity. Cardiac failure is not in itself a contraindication, but when it completely fails to respond to the usual therapeutic procedures it is an absolute contraindication. The electrocardiogram has been of value most frequently in verifying the diagnosis of recent myocardial infarctions. In such instances it has been our policy to defer operative intervention for eight weeks or longer depending on the severity and extent of the infarction. Evidence of marked left ventricular enlargement has been seen frequently and, other factors being equal, is an indication for operation. Improvement in the electrocardiographic tracing may be expected in a high percentage of cases.

Renal Status: Renal decompensation as reflected in elevated circulating nitrogenous wastes rules out the advisability of operation whatever the underlying renal pathology. In reviewing the operation and post-operative mortality data it is apparent that renal pathology as determined by elevated blood urea nitrogen above 18-20 mgm. per cent and N. P. N. above 40 mgm. per cent constitute one of the most reliable preoperative guides from the point of view of both immediate and remote prognosis in hypertensive patients. Of the fatalities, half the hospital deaths, and almost half the post-operative deaths also fell in this group. This is, of course, a gross test of renal competence, yet in our hands it has been highly reliable, especially in the absence of other gross evidence of renal damage, such as marked albuminuria, hematuria, anemia, etc. Borderline levels must be considered in the light of other findings and the surgeon has less confidence in making a decision the closer the levels are to the upper limits of normal. Poor concentration alone has not been considered a cause for exclusion. Urea clearance determinations were done routinely, but their reliability was frequently questionable due to the difficulty of adhering rigidly to the technical requirements of the test. Additional and perhaps more refined tests of renal competence would undoubtedly have revealed evidence of renal damage in other patients with established hypertension but for purposes of pre-operative evaluation their inclusion would seem to offer little of critical value. Intravenous pyelography was rarely of any value and was presently discontinued, except when clinically indicated.

In the pre-operative evaluation of the status of an organ, problems such as the following may arise: the renal concentration test may be

only 1.013, whereas the urea clearance may be 85 per cent of normal. In that case we have one test placing the kidney in a 3 plus category and the other in a 1 plus. We therefore, average the two and consider the degree of damage as 2 plus. Similarly a patient may have excellent cardiac function, that is, he may have no dyspnea, or angina after climbing three flights of steps and yet the electrocardiograms and chest plate may show moderate (2 plus) changes. It is a matter of judgment whether the patient should be classified as a 2 plus or 1 plus cardiac.

A complete blood count, a sodium amytal test (9 grains divided into three hourly doses) and a basal metabolism test are desirable but are not emphasized in evaluating the patient's status for sympathectomy. A high basal metabolic rate associated with the hypertension is suggestive of pheochromocytoma.

The response of the blood pressure to deep barbiturate sedation or the autonomic blockade, as by tetraethylammonium chloride, is a useful device for testing the capacity for relaxation of the arteriolar bed and theoretically anticipating the result. The sodium amytal test is a good indication of a probable post-operative blood pressure result but is not absolutely accurate as a prognosticator in any given case. In our series no patient was turned down solely on the basis of a poor response to sodium amytal.

The etamon test (tetraethylammonium chloride) has been studied by Poindexter and Tamagna[8] and compared with the sodium amytal test in over fifty patients and their report is in press. In approximately 75 per cent of the cases the two tests correlated exactly while in the remaining 25 per cent there was a variation in both directions. No post-operative evaluation of the usefulness of the etamon test has been made. In a group of ninety-four patients studied by Hinton and Lord[9] an immediate post-operative drop in pressure was obtained in a high percentage of cases that was consistent with the drop obtained with sodium amytal. However, in a significant group no consistent correlation was noted. The effect of autonomic blockade with tetraethylammonium chloride closely parallels the results obtained with sodium amytal.

Smithwick[10] has stated that patients with a hospital diastolic pressure of 140 and above do not respond satisfactorily to a thoracolumbar sympathectomy. Among twenty-four males with a diastolic pressure of 140 or higher he reports twenty deaths, three slightly improved, and

TABLE II

104 PATIENTS WHOSE DIASTOLIC PRESSURE EXCEEDED 150 MM. HG.

Dead				22
Hospital		13	12.5%	
H-V-D	9			
3-11	8			
18	1			
Follow-Up				82
0-6 mos.			36	
12			39	
24			17	
Inc. Op. Pro.			2	
Lost			5	

Mean Post-Operative Diastolic Pressures

Follow Up	*One Year*	*Two Years*
Resting	123 M.M. (39 Patients)	129 MM. (17 Patients)
Exercise	117 M.M. (35 Patients)	121 MM. (15 Patients)

one markedly improved. The results in our cases in this category are in variance with Smithwick's findings, as shown in Table II.

De Takats et al[11] have emphasized the importance of operation in patients under forty years of age having a diastolic pressure not exceeding 120 mm. of mercury. Our experience with the older group would seem worth recording and is presented in Table III.

OPERATIVE PROCEDURE

We place our patients in the exact lateral position with the lower leg flexed and the upper leg extended. The table is broken under the lower costal region. The tenth rib is resected subperiosteally in its entirety. The parietal pleura is then carefully reflected from the posterolateral chest wall, exposing the diaphragm which is divided in its entirety on the operative side. Retraction of the parietal pleura subdiaphragmatically with contained lung and retroperitoneal fat is facilitated by two large Harrington splanchnic retractors. Delineation

TABLE III

72 HYPERTENSIVES AGED 50-59 YEARS
SUBJECTED TO SYMPATHECTOMY

Dead						11						
Hospital			4	5.5%								
H-V-D			7									
3-6 Months	2											
7-12	3											
18-24	2											
Lost						3						
Summary of 58 Living Patients												
Follow-Up (Months)..	6		12			24			30		36	48
Patients	10		33			12			1		1	1
Resting 110—	6	60%	20	60%		8	66%		1		1	0
Diastolic												
Exercise 110—	9	90	20	60		7	58		1		0	0

of the greater, lesser, and least splanchnic nerves along the lower thoracic and upper lumbar sympathetic chain is not difficult because of the wide exposure. The greater splanchnic nerve is divided at its junction with the celiac ganglion. The chain is grasped with a long curved hemostat and carefully dissected from each intercostal artery and vein. The communicating rami are divided several millimeters from each ganglion and the chain is divided just below the third lumbar ganglion. The twelfth ganglion is usually located just above or in the substance of the diaphragm and we have repeatedly noted how attenuated the chain is between the twelfth thoracic and the first lumbar ganglion. The thoracic chain is pursued cephalad until the third ganglion is mobilized and division is carried out above it. In the majority of instances the greater splanchnic nerve has its origin from the thoracic ganglia 6th, 7th, 8th and 9th. The lesser and least splanchnic nerves are removed as the thoracic chain is mobilized. One of the interesting findings is the wide variation in the size and distribution of the nerves. The minimum operation in a series of 440 cases included 9 thoracic ganglia through the 2nd lumbar ganglion with removal of the greater, lesser,

and least splanchnic nerves. This represents about 40 per cent of the cases reported. The operative procedure is now much more extensive. In about twenty cases we have included the stellate ganglion through the third lumbar ganglion with all the splanchnic nerves. The operative procedure as we do it now includes the 3rd thoracic ganglion through the third lumbar ganglion with all the splanchnic nerves. It is obvious that the more radical the operation the higher the mortality, but also the better end results.

Precautionary Measures

As a result of our experience with 440 patients subjected to the two stage thoracolumbar sympathectomy during the past five and a half years, or from February, 1942, to August, 1947, certain principles of management during the operative and post-operative periods have evolved. These patients need every possible support to bring them through without a serious complication either due to their disease for example, coronary occlusion, heart failure, cerebral accident or renal failure or to a complication of thoracotomy such as pleural effusion, pneumothorax, atelectasis or pneumonia.

There are two basic problems to be handled during the operative and early post-operative periods: first, the maintenance of an adequate blood pressure, thereby avoiding a marked systolic fall to levels of 100 mm. of mercury or lower, which may occur with alarming suddenness, especially during and after the second stage procedure; and secondly, the management of the thoracotomy during and after operation. The maintenance of a relatively stable pressure has been best achieved by the use of 2 cc. of a 1 per cent solution of neosynephrine in 1000 cc. of 5 per cent glucose in distilled water administered intraveneously during the operation; and post-operatively, by using the same fluid with 1 cc. of neosynephrine per 1000 cc. of solution until the systolic blood pressure has become stabilized at 90 or 100 mm. of mercury or higher. This may take only a few hours or it may take as long as forty-eight hours. Before this method was introduced by Milton C. Peterson, head of the Department of Anesthesiology of the New York Post-Graduate Hospital, the anesthetist injected intramuscularly or intravenously 2 or 3 minims of neosynephrine when necessary and the same procedure was used post-operatively.

We have found that a moderate anemia develops after each stage of

the extensive sympathectomy, probably due to oozing into the extrapleural and intrapleural spaces during the early post-operative period. For this reason a 500 cc. blood transfusion is routinely administered immediately after each stage.

The second major problem is to secure hemostasis and to deal with the open thorax during the operation and to prevent serious hemothorax, pneumothorax, atelectasis, and pneumonia post-operatively. Grimson[12] has recently stated his position as follows: A closed anesthetic system is employed only occasionally using an intratracheal tube. The pleural cavity is deliberately entered through a partial 3rd rib resection and longer 10th rib resection and the chain removed from the stellate ganglion through L – 1 and L – 2 inclusive, followed by the use of a closed tube suction drainage of the pleural cavity for two or three days. We have also made use of a closed anesthetic system usually with an endotracheal tube. Recently we have begun a series without such a tube and the management in the hands of experienced anesthetists has been for the most part satisfactory. One point should be emphasized; this extensive sympathectomy should be carried out only when an anesthetist thoroughly familiar with open chest operative procedures is conducting the anesthesia. Although in our technique the parietal pleura is stripped from the chest wall from the diaphragm to the apex of the thorax it is usually torn to a greater or lesser extent so that air readily passes into the intrapleural space. The anesthetic agents used have been ether, cyclopropane, and ethylene, and their indications and contra-indications may be found in reports by Phelps and Burdick[13] and Burdick, Phelps, and Peterson.[14]

Hemostasis is not a simple matter in this procedure and one of the frequent complications has been development of fluid in the chest post-operatively. Grimson has had a similar difficulty by his method of approach. In addition to the clamp and ligature, there are at one's disposal temporary pressure on the venous bleeder against the vertebral column, which is often satisfactory; silver clips, oxycel and other hemostatic absorbable agents, bone wax and finally the electrocautery. We have not used the last mentioned because of the fear of an explosion in the presence of such potentially dangerous anesthetic agents and the open pleura. The most serious difficulty with hemorrhage is presented by an accidental tear of an intercostal artery high in the chest cavity such as the 3rd, 4th, or 5th. When hemostasis has been secured follow-

ing the removal of the sympathetic chain and suture of the diaphragm, the chest wall is closed around a large rubber catheter placed into the pleural space. Air is completely aspirated, the catheter removed and the skin closed without drainage.

During the entire post-operative period, but particularly during the first forty-eight hours, careful, repeated, bedside examination of the chest must be made. Signs of fluid and/or atelectasis (usually due to fluid) are promptly checked by a portable x-ray of the chest and aspiration with a large (number 15) needle carried out. In patients with poor cardiac reserve pleural effusion (usually hemorrhagic) may be of the gravest significance and prompt recognition and treatment may be life-saving.

Results

Though only one aspect of the disease-complex is represented in blood pressure readings they are useful as measurable end points. This is especially true of the diastolic pressure. Accordingly, we have summarized the results in 164 patients first by considering only the diastolic pressures, and by arbitrarily dividing our patients into two groups, those whose post-operative diastolic pressures were below 110 mm. Hg. and those whose diastolic pressures were above 110 mm. Hg. From this point of view, those in the latter group were considered to have a less than satisfactory result. Of the 164 patients followed for one year 93 had diastolic pressure of 110 or lower and 71 a diastolic pressure of above 110. A somewhat more dramatic response is demonstrated in the exercise column and is more steadily maintained for a longer period. We have been impressed by the number of patients whose post-operative diastolic blood pressure falls sharply after exercise, even when their resting pressure has been at higher levels. That this does *not* necessarily represent a good parallel with the effect to be expected from everyday stress and strain was apparent from the fact that frequently such sharp drops were seen in patients whose blood pressures, taken immediately after their walk or taxi ride to their appointment, were at higher levels. However, this paradoxical effect carries with it implications of benefit in those patients in whom vascular accidents might be anticipated when subjected to unaccustomed physical strain. The mechanism of such a drop in pressure may well be the result of peripheral dilatation in the muscle bed, unopposed as in the intact organism, by splanchnic con-

striction, thus averting the customary summated response of blood pressure elevation, as in the routine pre-operative response to exercise. The distribution of diastolic pressure drops, which is indicated in Table III demonstrates the significant difference between the resting and exercise results six months following sympathectomy.

Results in 104 Patients With Pre-Operative Diastolic Pressures Above 150 mm. Hg.

A review of 104 patients whose pre-operative diastolic pressures consistently ranged above 150 mm. Hg. is detailed in Table II. In this group, as might be expected, the immediate hospital mortality is significantly increased. The total number of deaths in the follow-up period at hand is high, but such an insignificant group has been followed for less than six months that further conclusions must be deferred. The range of diastolic pressure results is so broad as to preclude critical analysis from the point of view of pre-operative prognosis.

That relatively advanced age is not necessarily a contra-indication to thoracolumbar sympathectomy is readily appreciated in reviewing the data in Table III which represents the operative results in a group of 72 patients from 50 to 59 years of age. The hospital death rate was lower than that of the group as a whole, and the two-year follow-up reveals a large percentage of the patients continuing to maintain a satisfactory diastolic level. Though this group would ordinarily be expected to include a higher percentage of patients with chronic vascular changes, intensive clinical study was undertaken to eliminate those with such changes and undoubtedly the results in this group are highly colored by fortunate clinical pre-operative evaluation.

Toxemia of Pregnancy

We do not have at hand the data in a sufficiently adequate series to formulate an opinion on the relation of hypertension to the toxemia of pregnancy and the operative results. Of interest, however, are two young women in their early twenties, one with well documented hypertension of undetermined etiology, who following operation went through a full term pregnancy with an entirely normal blood pressure. The other developed hypertension during a previous pregnancy in the course of a mild toxemia, her subsequent blood pressure being in the range of 230/140 mm. Hg. One year following the day her second

TABLE IV

SUBJECTIVE AND OBJECTIVE END RESULTS OF OPERATION

No. of Patients	*Follow-Up Period (Mos.)*	*Subjective Improvement*		*Marked and Moderate Objective Improvement*	
215	6	163	76%		
148	12	123	83%		
76	18	62	81%		
62	24	50	80%		
152	6			123	81%
69	12			62	90%
31	18			28	90%
15	24			11	73%
8	36			8	100%

*This evaluation is based on post-operative blood pressure: electrocardiographic readings, heart X-ray, blood chemistry, urinalysis, and symptomatic improvement.

stage operation was completed she delivered a full term viable infant, having maintained a normal blood pressure throughout her pregnancy. These are, of course, isolated observations, but are noted for their clinical interest.

SUBJECTIVE RESULTS

From the clinical point of view a most important consideration in the evaluation of any therapeutic procedure is the subjective result obtained. Our experience has paralleled that of others, in that we have consistently been impressed by the subjective improvement and the disappearance of severe and often disabling symptoms irrespective of the effect on the blood pressure. In obtaining these opinions from our patients, in all instances, a nurse-technician has asked them, among other questions, "Has the operation, in your opinion, benefited you?" Many factors enter into such a personal reaction. The patients may have had such a miserable post-operative course that the natural recovery from its severe discomfort leaves them uncertain that they are now better. Less easy to discount is the almost inevitable relief from pounding headaches and a sense of "relief from tension" not unlike that sensation so often described by patients who have undergone subtotal thyroidec-

tomy for hyperthyroidism. Details of the subjective results among 215 patients are tabulated in Table IV and compared with objective improvement in 152 patients of another group.

The Overall Picture

As noted in reviewing the older age group, the final selection of patients for operation is highly colored by what, for lack of a more suitable term, we call clinical judgment. Difficult though this is to define quantitatively, nevertheless the clinical impression of a patient, to some extent, equals the sum of the effects of the disease processes at work plus the evidence of the force of the patient's particular psychology and physiology working in opposition to the disease processes. It is a common clinical observation that there are times when the patient looks better than the chart would indicate, and vice versa. We feel that most clinicians will agree, especially in the face of equivocal or conflicting laboratory findings, that such an overall evaluation of the patient must continue to play a significant part in the final decision for or against operation.

Summary

In a five-and-a-half-year period, or from February, 1942, to November, 1947, there have been 455 patients operated upon for essential hypertension and most of these patients have fallen in the advanced stages of hypertensive disease. Among these patients, there were 183 males and 272 females. The total deaths in and out of the hospital from February, 1942 to November, 1947, were 74 or total mortality of 16 per cent. The causes of deaths occurring in the hospital were in the following order: cerebral, cardiac, and renal. The out-of-the-hospital deaths are in the following order: cardiac, cerebral, and renal.

One should clearly differentiate, in evaluating the end results, whether surgery has been done for the cases in the early stages of hypertensive disease or in the advanced stages of hypertensive disease. Obviously, both the in and out of the hospital mortality changes entirely depend on which type of case one is discussing.

At the present time we feel that thoracolumbar sympathectomy has a definite place in the treatment of hypertensive vascular disease, but its role in advanced cases is chiefly a palliative procedure. The overall end results in the advanced cases of essential hypertension, will give,

both from the point of view of comfort and life expectancy, a better follow-up than surgery done for carcinoma of the thyroid, breast, stomach, or large intestine whether the carcinoma cases are early or late.

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MORPHOLOGICAL BASIS FOR MENSTRUAL BLEEDING*

Relation of Regression to the Initiation of Bleeding

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INTRODUCTION

ANY attempt to discuss menstruation engenders the feelings of humility and incompetence. The humility arises, at least in part, from the limitations which prevent giving credit where credit is due to the many investigators who have contributed to our present knowledge of menstruation and the menstrual cycle. The feeling of incompetence results partly from the inability to correlate all of the observed facts and weave them into any one completely satisfactory theory of menstruation. Therefore with the realization that this description must be far from complete and satisfactory, I have compromised by restricting the narrative to little more than what one can see happening in endometrium that has been transplanted to the anterior chamber of the eyes of a monkey. Most of the evidence supporting a morphological explanation for menstrual bleeding has been presented elsewhere,[1,2,3] and I should like to spend the time allotted to me primarily in marshalling the evidence which indicates that regression or rapid decrease in the thickness of the endometrium initiates the chain of events leading to menstrual bleeding. However, before attempting to show where regression fits into the total picture it seems advisable to summarize the events which occur during a menstrual cycle.

The interrelated changes in the hypophysis, ovaries, blood and endometrium may be considered first. The interrelationship may be most easily followed by beginning with the degeneration of a corpus luteum or ovarian follicle. As a result of the decreased blood estrogen, the anterior lobe of the hypophysis liberates F.S.H., which causes the development of additional ovarian follicles and the secretion by them

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of estrogen. Their secretion may cause the slight rise in blood estrogen at about the middle of the menstrual period. However, the maintenance of the blood estrogen at about 30 I.U. per liter until about the tenth day of the cycle must be due to three factors: 1) the significant, although decreased, secretion by the degenerating follicle or corpus luteum of the previous cycle; 2) secretion by the newly formed follicles; and 3) secretion by the "chosen" follicle of this cycle. As the "favored" follicle grows, it produces more estrogen which acts back upon the anterior lobe of the hypophysis and causes the liberation of LH and probably also luteotrophin. The former causes the final growth spurt of the follicle, ovulation and the development of a corpus luteum; the latter, probably as in the rat, causes the formed corpus luteum to secrete progesterone and estrogen. Thus, the secretory activity of the corpus luteum maintains the blood estrogen level and raises the blood progesterone level to about 75 mg. per liter of urine by the twentieth day of the menstrual cycle. Soon thereafter the corpus luteum begins to degenerate, and the concentrations in the blood of progesterone and estrogen decrease. The hypophysis responds by producing more F.S.H. to initiate a new cycle.

The changes in the blood level of estrogen and progesterone may be correlated with endometrial growth in the following way. A blood estrogen level of 30 I.U. per liter in the experimental monkey, and presumably in the human, is adequate to stimulate the amount of endometrial growth that normally occurs between the end of the menstrual period and the time of ovulation. Since the blood estrogen concentration is about 30 I.U. per liter during the few days before menstruation, as well as for a number of days after the end of the menstrual period, it must follow that the preovulatory growth is not due to an increase in the blood estrogen level but to the pre- and postmenstrual level of 30 I.U. which is high enough to induce the preovulatory growth of the endometrium.

The rise in the blood estrogen on about the tenth day of the cycle and the secretion of progesterone seem adequate to produce even more growth than normally occurs in the postovulatory period.

Elsewhere[3] attention has been called to the differences in behavior of the capillaries supplying the three following zones in the endometrium: 1) the general stroma; 2) the glands supplied by basket-like capillaries; and 3) the subepithelial meshwork of sinusoidal capillaries. In

the former, the rise in blood estrogen causes an increased rate of flow and probably a sufficiently elevated pressure to produce the estrogen-induced edema described by Astwood,[4] and Williams.[5] The increased caliber of the basket-like capillaries around the uterine glands is apparently a characteristic response in the monkey as it is also in the rat.[5] The behavior of the subepithelial sinusoids is still incompletely understood; it deserves further study, in part at least, because of its extreme variability which tempts one to believe that it may give a clue to other unrecognized variables.

The blood estrogen declines sharply on about the twentieth day and drops from around 60 I.U. to about 30 I.U. per liter on around the twenty-fourth day. During this period the progesterone level also drops precipitiously. In the monkey comparable decreases have been induced experimentally (from 45 to 20 I.U. per liter), and the decrease in the area of the intraocular endometrial transplants parallels that which occurs in the endometrial transplants during normal menstrual cycles. It therefore seems reasonable to conclude that the decrease in the thickness or regression of the endometrial transplants is due to the withdrawal of the growth stimulus supplied by estrogen and progesterone.

The manner in which the withdrawal of the growth stimulus produces regression is incompletely understood. However, it has been demonstrated that the withdrawal of estrogen slows the rate of flow through the stromal capillaries[3] and thereby reduces at least one of the forces that drives fluid from the capillaries into the stroma. This shift in the equilibrium between the fluid entering and leaving the stroma should cause a withdrawal of fluid from the stroma and endometrial regression. This may represent a part of the mechanism whereby a lowered estrogen level induces regression.

Similar measurements on the rate of flow in the basket capillaries around the endometrial glands have not been completed. Nevertheless many direct observations indicate that there is a marked reduction in vascularity and blood flow to the glands after the withdrawal of progesterone. This may be the cause of collapse of the uterine glands and, also, the mechanism by which the withdrawal of progesterone leads to menstrual bleeding.

Vascular Changes Preceding Hemorrhage

The vascular changes described immediately above occur after the

estrogen or progesterone level has been decreased. They occur also in non-primate mammals and hence are not distinguishing characteristics of a menstrual cycle. On the other hand, the two following vascular changes, relative *stasis* and *vasoconstriction*, are apparently restricted to the primates. Beginning one to five days before the onset of menstruation, there is a period of slowed circulation or relative stasis, this is followed by a period of vasoconstriction which begins 4 to 24 hours before the escape of any blood.

The *period of stasis* begins after the area of the transplants has decreased 20 to 30 per cent. The circulation in the region of the transplants supplied by the coiled arteries becomes slower and slower until the erythrocytes move so slowly in the capillaries that a condition of stasis or near stasis exists. Frequently the erythrocytes do not move for 60 to 90 seconds and a distinct bluing of the transplants is noticeable with the naked eye. The stasis apparently is caused by the increased resistance to flow resulting from the increased coiling of the arteries. The duration of the period of stasis is extremely variable. In those cycles in which 63 to 76 per cent of the decrease in the areas of the transplants occurs before menstruation begins, stasis begins at least four days before the onset of the menstrual flow. If half of the regression has been completed before menstrual bleeding, stasis is present for at least two days. If less than half of the decrease in the area of the transplants precedes menstruation, stasis occurs for less than two days, and if as little as one-fourth of the regression occurs before menstruation begins, the period of stasis is less than twenty-four hours long.

Vasodilatation, which sometimes occurs during the period of stasis, is extremely variable as to both incidence and intensity. It was not observed at all in 55 per cent of the cycles, but when present, began during the first or second day of the period of regression, before the onset of bleeding and after the area of the transplants had decreased 20 to 30 per cent. It was most marked in those cycles in which there appeared to have been an interval between the end of growth and the onset of regression. However, when growth had continued at a rapid rate until regression began, vasodilatation was not observed. Dilatation occurred in ovulatory and anovulatory cycles during the breeding season and was observed in an occasional cycle during the nonbreeding season. Vasodilatation of the subepithelial sinusoidal-like capillaries caused by activity of the a-v anastomosis has been advanced by Okkels

and his collaborators[6] as the cause of menstrual bleeding. However, it should be reëmphasized that vasodilation was not observed in 55 per cent of the 432 menstrual cycles.[1] It therefore seems obvious that in 55 per cent of the cycles studied vasodilation could not have been the cause of menstrual bleeding.

The *period of vasoconstriction* preceding the onset of menstruation is the most striking and constant event in the menstrual cycle. It precedes every menstrual period, always beginning four to twenty-four hours before the onset of the bleeding. The coiled arteries that supply the blood to the superficial two-thirds of the transplants contract and blood may remain in the arterioles, capillaries, and veins for seconds or minutes; then the erythrocytes drain out of the arterioles, the capillaries, and finally the veins. After the vasoconstriction has begun, the superficial half to two-thirds of the endometrium receives an inadequate blood supply during the remainder of that menstrual cycle. The anemic appearance of the functional zone of the endometrium is in striking contrast to that of any other tissue. The fact that a tissue which is to bleed for about four days can be so bloodless for four to twenty-four hours beforehand and throughout the period of bleeding still seems enigmatic, even after having been observed throughout 432 menstrual periods. Within a period of one to five hours one coiled artery after another contracts until all those in the transplant are constricted. All the coiled arteries in one transplant may be contracted for two days before any in another transplant in the same eye begin to contract. The lumen is almost completely obliterated in the deepest part of the basal zone, though a few erythrocytes per minute pass the region of constriction. Distal to this region the diameter of the lumen varies between 15 and 30 micra, but the passage of only about fifty erythrocytes per minute through an artery supplying a vascular field with an area of four to seven sq. mm. must indicate constriction. When the blood flow is temporarily reëstablished, bleeding occurs. Blood escapes soon after the coiled arteries relax, and continues to do so as long as circulation persists through them.

It has previously been pointed out[1] that a number of lines of evidence indicate that a product of endometrial degeneration may be absorbed systemically during endometrial regression, and that the substance may be the cause of the constriction of the basal portion of the coiled arteries. This hypothetical substance may be in fact the

menstrual toxin investigated by Smith and Smith[7] and this may be identical with the necrosin studied by Menkin.[8] The latter substance when injected into endometrial transplants causes constriction of the arteries.[2] It therefore seems probable that the vasoconstriction is caused by this product of endometrial regression. When the local concentration of this substance decreased an individual coiled artery would no longer be stimulated to contract and therefore would relax and bleeding occurs from the weakened coiled artery or its branches. The hemorrhage would be terminated when the concentration of this product of endometrial degeneration increased in the region of the coiled artery sufficiently to stimulate it to constrict again.

Types of Hemorrhage

Menstrual bleeding occurs when blood escapes from one of the branches of a coiled artery which has been constricted for a number of hours. Five types of menstrual bleeding were observed in the transplants: 1) blood that escapes through a break in the wall of an arteriole or capillary may form a hematoma which ruptures, or 2) it may break through the uterine epithelium and escape into the anterior chamber of the eye without forming a hematoma; 3) diapedesis may occur through the wall of a capillary and the escaping blood may or may not form a hematoma; 4) there may be either a direct flow or a reflux of blood from the veins in the fields of previous hemorrhage and destruction of tissue; and 5) secondary bleeding may occur from an arteriole following experimentally induced fright or violent movement. A detailed description of these five types of bleeding in the transplants has been presented elsewhere,[1] and it should suffice here to reëmphasize (a) that bleeding occurs only when the basal portion of a coiled artery relaxes and (b) that the individual hemorrhages are arrested when that portion of the artery again constricts. One of the most spectacular events one can witness is the hemorrhage from a naked artery protruding above the surface of the endometrium and the termination of the hemorrhage when the basal part of that artery constricts.

Relation of Regression to Induction of Menstrual Bleeding

It has already been pointed out that regression is the first of the events which precede menstrual bleeding in both ovulatory and anovulatory menstrual cycles. The length of the period of premenstrual

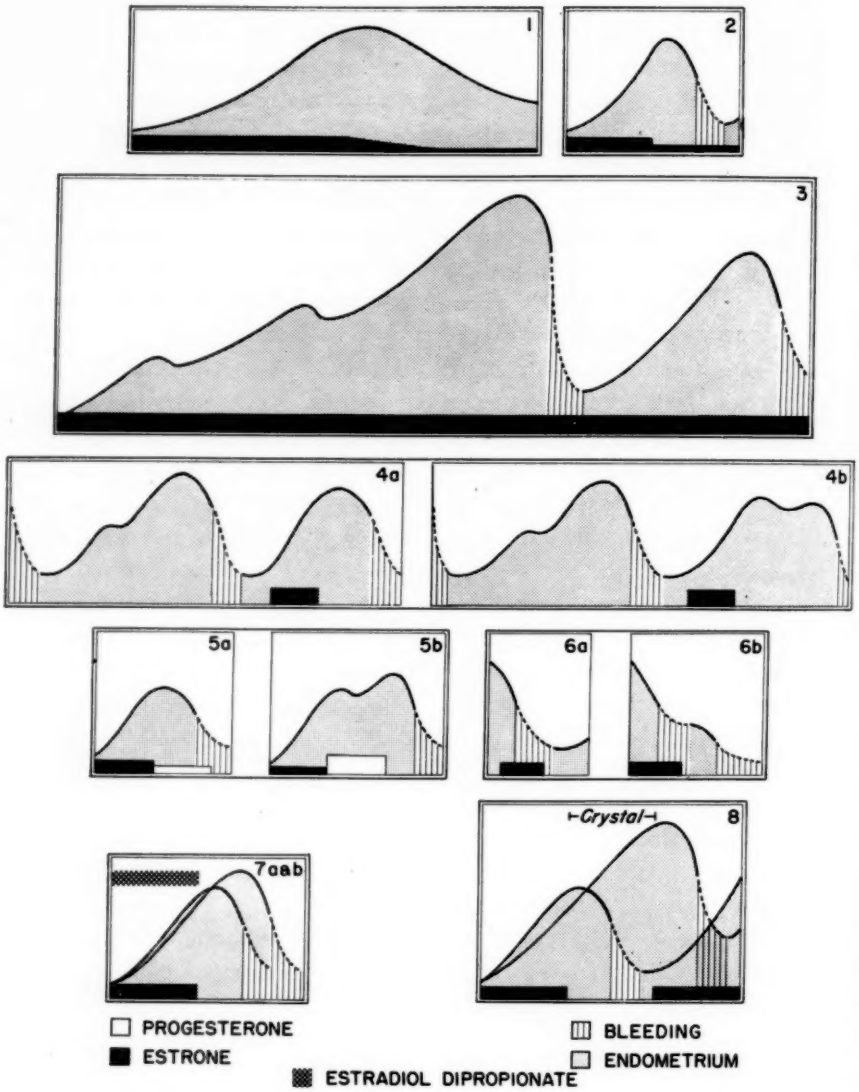
regression and the amount of regression that precedes bleeding varies in different cycles (25 per cent to 76 per cent). However, in general, the transplants that have grown most regress most, and the rate of regression is greatest in them. Since in all spontaneous cycles regression always precedes menstrual bleeding, the following eight types of experiments (Fig. 1 to 8) were carried out in an attempt to elucidate some of the relations between regression and menstrual bleeding.

I. *Induction of Slow Regression Without Menstruation.* Gradual regression without menstruation was induced by injecting about 250 R.U. of estrone a day and then gradually decreasing the daily dose to about 25 R.U. When the dosage is reduced by about 1/20 per day a slow regression without menstruation may be induced (Fig. 1).

It was found that slow regression of the transplants and of the uterus without menstruation could be induced by gradually decreasing the daily dosage of estrone, but slow regression without bleeding also occurred in uninjected and apparently normal monkeys without menstruation during periods of amenorrhea. It is possible that these periods are caused by a very slow decrease in the estrone level, as they resemble the experimentally induced slow regression not associated with menstruation. That variations in the estrone content occur during amenorrhea in woman was reported by Fluhmann.[9] The present experiments demonstrate conclusively that time is extremely important in the response of the uterus to estrone and that the injection of a constant amount of it continues growth rather than maintains the endometrium at constant size.

II. *Menstruation Induced by Halving the Estrogen Level.* Since gradually decreasing the daily dosage produced a slow regression without menstrual bleeding, the size of the transplants were measured and graphed in experiments during which the daily dose of estrogen was suddenly decreased by 50 per cent (Fig. 2). Decreasing the daily injection of estrogen from 250 to 125 R.U. induces rapid regression of the endometrial transplants and bleeding in them that is indistinguishable from that following complete estrogen withdrawal. It should be emphasized that in this experiment only one-half as much estrogen was withdrawn as in the previous experiment but that it was withdrawn suddenly rather than over a period of eighteen days.

III. *Menstruation During a Long Series of Injections of Estrogen.* Menstruation will occur during a long series of injections of estrogen.



(SEE NEXT PAGE FOR LEGENDS)

Bleeding under these conditions was reported in the rhesus monkey by Corner,[10] Hartman,[11] and Engle, Smith and Shelesnyak,[12] and in man by Werner[13] and by Bowman and Bender.[14] The transplants were, therefore, observed during a long course of daily injections of estrone to determine whether this bleeding was preceded by regression and the other events which normally precede menstruation and in what respects, if any, they differed from the normal. Figure 3 illustrates the change in the area of endometrial transplants during a series of 93 daily injections of 250 R.U. of estrone. Slight regression occurred on days 15 and 34 and marked regression on days 64 and 82. In this and other similar experiments[1] slight or slow regression is not followed by menstruation, but rapid and extensive regression did precede every period of menstrual bleeding that occurred during a long series of injections of estrogen.

In this experiment, fluctuation in the estrogen level was eliminated as a causative factor in the menstrual bleeding. In this experiment, as in previous ones, rapid regression appears to be the first of the sequence of events leading to menstrual bleeding.

LEGENDS

Figures 1 to 8 illustrate the relation between rapid endometrial regression and menstrual bleeding.

Fig. 1. Slowly decreasing the estrogen dosage by 9/10 is not followed by menstrual bleeding.

Fig. 2. Rapid decrease of the estrogen level by 1/2 is followed by rapid regression and bleeding.

Fig. 3. The menstrual bleedings that occur during a long series of estrogen injection (93 days) are preceded and accompanied by rapid endometrial regression.

Fig. 4. When the end of a series of injections of estrogen during the primary growth period is followed by rapid regression, bleeding occurs (a) but in this phase of the cycle menstruation does not follow estrogen withdrawal in the absence of rapid endometrial regression.

Fig. 5. Estrogen withdrawal bleeding does not occur during a subsequent series of injections of progesterone if enough progesterone is injected to continue endometrial growth, (b) but does occur if the dosage of progesterone is inadequate to prevent rapid endometrial regression (a).

Fig. 6. If the estrogen injected during menstruation and its withdrawal is followed by further rapid regression a secondary period of bleeding occurs (b).

Fig. 7. Although the interval between the withdrawal of different kinds of estrogen varies (estrone in lower curve and estradiol dipropionate in upper curve), the interval between the onset of regression and bleeding appears to be fixed.

Fig. 8. The lower curve indicates that the transplants in the untreated eye responded to the systemic changes in estrogen. The upper curve illustrates the growth of the transplants in the eye into which crystalline estrogen had been inserted and the rapid regression and bleeding of the transplants in that eye after the removal of the crystalline estrogen.

IV. *Injection of Estrogen During the Primary Growth Period.* In six experiments the growth of the endometrial transplants was followed after the injection of estrogen during the primary growth period (day 7 to 14). In all six monkeys the injection of 250 R.U. of estrone a day during the second quarter of the menstrual cycle caused more growth than usual and nearly as much as normally occurs near the end of the cycle.

Withdrawal of estrone was followed by regression which was slight after little, but extensive after marked growth. Estrone withdrawal terminated the growth and menstrual cycles under way, and whenever its withdrawal was followed by slight regression and arrested growth no bleeding was induced (Fig. 4b) but when regression was rapid and extensive, menstruation preceded a new cycle of growth (Fig. 4a). When it was slight the intermenstrual interval was lengthened to fifty, thirty-seven and forty-four days, but when it was extensive bleeding occurred in six to eight days.

These experiments supply additional evidence indicating that 1) endometrial regression is not always followed by menstruation and 2) menstruation occurs only when regression is rapid and extensive.

V. *Bleeding After the Withdrawal of Progesterone.* If a series of injections of progesterone is begun immediately after the withdrawal of estrogen, the bleeding which usually follows the withdrawal of estrogen may or may not be prevented. In a series of eight experiments graded doses of estrogen were followed by graded doses of progesterone (two examples are shown in Figure 5a and b). When the amount of progesterone given following the last injection of estrogen was large enough to cause the continuation of endometrial growth, menstruation and all the usual evidences of imminent menstrual bleeding were inhibited as long as the injections of progesterone were continued. On the other hand, when the dosage of progesterone was inadequate to continue the growth caused by the estrogen, regression was the first of the events leading to menstruation during the injection of progesterone. These experiments certainly do not throw any light on the question of the relative roles of estrogen and progesterone during the menstrual cycle. However, they do indicate that menstruation is initiated by rapid regression rather than by either of the ovarian hormones.

VI. *Injection of Estrogen During Menstruation.* If large amounts

of estrogen (250 to 500 R.U. per day) are injected during menstruation, the bleeding may occur without apparent alteration (Fig. 6a), or regression may be slowed (Fig. 6b). The latter happened in five out of nine such experiments. The regression which normally occurs during bleeding was slowed, and a second period of regression and an estrogen-withdrawal bleeding occurred after the injections of estrogen were discontinued. The explanation of the secondary bleeding following the withdrawal of estrone, when regression is slowed by injections of it just before and during menstruation, is suggested by the following observations. Since the straight arteries supplying the basal portion of the transplants carried more blood during estrogen delayed regression than in normal menstrual periods, it is possible that the greater amount of blood supplied to the basal portion of the transplants caused the delay. The second observation which may be related to the delayed regression is the growth of some of the dilated straight arteries and the differentiation of some of them into coiled arteries. Moreover, whenever regression was re-initiated, new coiled arteries formed from the straight ones in the basal bed, and menstruation ended when there was an increased blood flow through the basal vessels. The appearance of this phenomenon in different transplants in the same animal was as variable as the time of onset of the vasoconstriction. Since the injection of estrone during the primary bleeding caused increased circulation in the basal vessels, regression was slowed or arrested and less tissue destroyed, but regression was resumed after the withdrawal of estrone; additional coils formed in some arteries which had been spared; stasis and further destruction of tissue occurred; and blood escaped from the injured vessels. These observations may explain the secondary bleeding.

Injection of Progesterone Just Before and During Menstruation

In a series of eight experiments the injection of progesterone was begun after changes in the endometrial transplants indicated that menstruation was about to begin (the events which enable one to foretell menstruation are described elsewhere[1]). In these experiments the first injection was given six, eight, eight, nine, thirteen, fifteen, sixteen and nineteen hours before the beginning of menstruation, and the dosage ranged from 2 to 10 mgm. of progesterone per day. The smaller doses had no apparent effect on the menstrual bleeding. However, the larger doses slowed regression and shortened the menstrual periods. In these

instances a period of withdrawal-bleeding began four to six days after the last injection of progesterone.

These facts demonstrate the intimate relationship of menstrual bleeding and endometrial regression. They indicate but do not necessarily prove that regression causes menstrual bleeding. It is still possible that both regression and bleeding are caused by a common factor or that a hypothetical substance which may cause menstrual bleeding can do so only during regression. Regression causes a disproportion between the length of the coiled arteries and the thickness of the endometrium, and this in turn appears to cause the development of additional coils, increase the resistance to the flow of blood through these arteries, and result in stasis which may cause the degeneration of the functional zone of the endometrium. Constriction of the coiled arteries does not appear to be related to the causation of menstruation but instead appears only to control blood loss from the damaged vessels.

VII. *Comparison of the Effect of Different Kinds of Estrogen on Withdrawal Bleeding.* An additional means of critically checking the hypothesis that regression is the phenomenon initiating the chain of events leading to menstrual bleeding was made available by the finding that in the rabbit regression is delayed longer after the last injection of estradiol dipropionate (Ciba) than after the injection of estrone. Therefore, if in the monkey an equally long interval were to elapse between the last injection of estradiol dipropionate and the beginning of regression, and yet if bleeding were to begin as soon after estrone withdrawal, menstruation should commence before the onset of regression.

Consequently three groups of monkeys, six in each group, received estradiol dipropionate. Instead of disproving the hypothesis, all eighteen experiments resulted as follows: menstruation began ten to thirteen days after the withdrawal of estradiol dipropionate, that is, four to nine days later than after withdrawal of estrone (Fig. 7). The following evidences of regression were observed in each of the eighteen experiments: decrease in the swelling and color of the sex skin; decrease in the intensity and distribution of the "washboarding"; a variable decrease in vaginal desquamation; increased coiling and buckling of the coiled arteries; venous and arterial stasis with or without vasodilatation; leukocytic infiltration; and finally vasoconstriction.

The most striking characteristic of all eighteen experiments is the

markedly delayed onset of endometrial regression after the withdrawal of estradiol dipropionate. Furthermore, the amount of delay in the bleeding in all these experiments was identical to the amount of delay in the onset of regression, the bleeding beginning about as soon after the onset of regression in the monkeys treated with estradiol dipropionate as in those from which estrone had been withdrawn. Therefore, these experiments supply further evidence indicating that extensive and rapid regression is the phenomenon which initiates the chain of events leading to menstrual bleeding. The next experiments to be reported demonstrate that when regression is induced only in the transplants in one eye, bleeding occurs in them, but not in the transplants in the other eye or in the uterus. If regression and menstrual bleeding are due to a common factor, that factor must act locally, since menstruation may occur even though the systemic estrone level is being raised.

VIII. *Local Control of Menstrual Bleeding.* Endometrial transplants in the anterior chamber of the eyes of monkeys offer an opportunity of determining whether menstruation is caused by systemic changes or by local changes in the endometrium. By introducing a crystal of estrone into one eye of a monkey which had transplants in both eyes it is possible to expose the transplants in the two eyes to different concentrations of estrogen. Those conditions permitted three types of experiment: 1) the concentration of estrone may be raised in one eye; 2) the systemic estrone level may be decreased while the crystal maintains a high concentration in one eye; and 3) the relative concentration in one eye may be decreased by the removal of the crystal, while the systemic level is being raised.

In the first type of experiment a crystal of about 0.6 mgm. of crystalline estrone was introduced into one eye of an ovariectomized monkey whose uterus and transplants had reached a base level. About four times as much growth occurred in the transplants in the eye containing the crystals as in the other eye but sufficient estrone entered the systemic circulation to cause some growth in the transplant in the other eye and in the uterus. The second and the third type of experiment may be carried out on the same monkey as follows (Fig. 8). At the end of a series of injections of estrogen a crystal of estrogen may be introduced into one eye. The transplants in the untreated eye and the uterus regress and bleed because of the lowered systemic estrogen level. On the other hand the transplants in the treated eye continue to grow. In the

third type of experiment the relative concentration in one eye may be decreased by the removal of crystals, while the systemic level is being raised by the injection of estrogen (Fig. 8). Under these conditions the transplants in the untreated eye and the uterus grow but the transplants in the eye from which the crystals have been removed regress rapidly and menstruate.

Failure of menstruation in the transplants in the eye containing the crystals while it is occurring in those in the other eye and in the uterus, owing to the lowered blood estrone level, may be interpreted in at least two ways. If menstruation is caused by a specific bleeding substance or hormone, the failure of such transplants to bleed may be due to a "protective" action of the high concentration of estrone in that eye; or, if it is due to local action during regression or to some local change caused by regression, the transplants may fail to bleed merely because they are growing rather than regressing.

Menstruation in transplants in the eye from which the crystals of estrone had been removed while the transplants in the other eye and the uterus were growing cannot be explained by a specific substance or hormone which causes bleeding, for the level of estrogen in the blood was rising. The stimulus for the bleeding in these transplants must be a purely local one, for the removal of the crystals suddenly decreases the concentration of estrone in that eye, although the systemic level is being raised by the estrone injected subcutaneously. The endometrium may be made to grow or regress, and to bleed when the systemic estrone level is rising or falling, but bleeding occurs only in those areas in which there is rapid and extensive regression. If these experiments be considered by themselves, it would be permissible to attribute the experimental bleeding to local deprivation of estrone, but menstruation can be induced in other ways, such as by the withdrawal of the corpus luteum hormone and by spinal transection. The factor that seems to be common to menstruation in transplants and uterus, no matter how induced, is rapid local endometrial regression, which it seems logical to assume is the phenomenon which initiates the chain of events leading to degeneration and bleeding. If this be correct, inquiry into the restriction of menstruation to primates need not be directed to a specific bleeding hormone, but to something that happens during regression in the endometrium of only the primate uterus.

In the primate during local regression the endometrium becomes

thinner more rapidly than the coiled arteries shorten. A disproportion hence develops and apparently is the cause of the further coiling, stasis, degeneration, and bleeding. Since the constriction of the coiled arteries preceding the onset of bleeding appears sufficiently intense to cause degeneration and bleeding, one theory of the causation of menstruation has been based on that observation. However, even when menstruation was induced in only the transplants in one eye, marked degeneration preceded the vasoconstriction and it appeared that the degeneration was caused by stasis and that the vasoconstriction, preceding and accompanying bleeding, merely prevented the excessive loss of blood from already weakened vessels, for after the onset of vasoconstriction bleeding occurred except when all the coiled arteries were contracted.

Summary

Eight lines of evidence are presented which indicate that rapid regression is the phenomenon which initiates the chain of events leading to menstrual bleeding.

1. If the estrogen level is slowly decreased by 9/10, a slow regression occurs that is not accompanied by menstrual bleeding.

2. If the estrogen level is suddenly decreased by 1/2, rapid regression and bleeding occur.

3. The menstrual bleedings that occur during a long series of injections of estrogen are preceded and accompanied by rapid regression.

4. When the end of a series of injections of estrogen during the primary growth period is followed by rapid regression menstruation also occurs.

5. Estrogen withdrawal bleeding does not occur during a series of injections of progesterone if enough progesterone is injected to continue endometrial growth, but does occur if the dosage of progesterone is inadequate to prevent rapid endometrial regression.

6. If the estrogen injected during menstruation slows regression and its withdrawal is followed by further rapid regression a secondary period of bleeding occurs.

7. When comparable amounts of growth have been induced, the interval between the withdrawal of different kinds of estrogen and the onset of bleeding varies; the interval between the onset of regression and bleeding appears to be fixed.

8. It is possible to cause continued growth of the transplants in one eye during systemic estrogen withdrawal and also local regression and menstrual bleeding in the transplants in one eye at a time when the systemic estrogen level is being increased. This experiment and the preceding ones indicate that local rapid endometrial regression is the phenomenon which initiates the chain of events leading to menstruation.

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